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CARBON-13 MAGNETIC RESONANCE ANALYSIS IN NITROGEN HETEROCYCLIC COMPOUNDS

BY

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"CARBON-13 MAGNETIC RESONANCE ANALYSIS
IN NITROGEN HETEROCYCLIC COMPOUNDS"

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獻給至愛的父母親

TO MY PARENTS

ABSTRACT

The carbon-13 magnetic resonance spectra of 6 Vinca alkaloids, 2 indole-vindoline dimers and 11 Strychnos alkaloids have been determined. Spectroscopic techniques (off-resonance and selective decoupling), additivity relationships derived from chosen model compounds (see below), and intercomparisons of carbon-13 shift values within structurally related systems were used to obtain self-consistent and unambiguous assignments for almost all the resonances in these systems. The analyses show that our cmr spectroscopy can be a useful tool for structural and conformational studies of complex alkaloids.

The present study also involved the use of carbon-13 nmr as a probe into both configuration and conformation in saturated nitrogen heterocycles, ranging from 3- to 9-membered ring size. Experimental data show that protonation, methylation, methiodation and oxidation of the nitrogen atom produce specific and additive effects on the carbon-13 chemical shifts of the ring carbons. Substituent effect parameters have been derived for all of these systems and compared with those obtained in earlier studies on the piperidines and cyclohexanes. The parameters show greatest deviations in the 7-, 8-, and 9-membered ring series, a feature attributed to increased steric factors. Attempts have been made to

assign conformations to these larger heterocycles on the basis of the observed substituent effects. In addition, the derived parameters were applied to aid in the assignments of the indole and dihydroindole alkaloids studied.

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I INTRODUCTION

A. Objectives of this Research

The aspect of configuration and conformation is essential to the determination of structure in naturally occurring compounds or their synthetic intermediates. Proton magnetic resonance (pmr) spectroscopy has proven to be useful in determining and confirming structural assignments for low molecular weight systems but does not greatly facilitate structural and conformational studies of complex molecules, such as alkaloids, which often give highly complex unresolved pmr spectra. Carbon-13 nuclear magnetic resonance (cmr) spectroscopy [1-5] has shown promise in these areas. In the present work we have studied the indole alkaloids of strychnine, cleavamine and cleavamine-vindoline dimeric type. The structural complexity and diversity within each separate family provide an ideal test for the validity of the statement that cmr is a better structural tool than most other physical methods. It has been shown that self-consistent and unambiguous assignments of nearly all the resonances for the above alkaloids are made feasible by application of the chemical shift additivity relationships based on simpler constituent molecular species. Intercomparisons of carbon-13 shielding values within structurally related systems in conjunction with suitable model compounds, such as piperidines, hexamethylenimines, octamethylenimines, N,N-dimethyltryptamine and 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene. The cmr analysis provides considerably more insight than previously available regarding structure and conformation in the alkaloids studied.

The present study includes saturated nitrogen heterocycles of the 3- to 9-membered ring type along with their hydrochloride salts, N-methylated derivatives, methiodides, N-oxides and some deuterated methiodides, in particular, of the 5- to 9-membered ring type. The compounds were synthesized and purified by conventional techniques. Carbon-13 additivity parameters have been derived for the various substituents within this series. Ring size, strain and conformation are shown to be significant factors in modifying the observed parameters. The effect of protonation, N-oxidation and methiodation were found particularly useful in the assignment of many of the indole alkaloids studied.

B. General Considerations and Historical Development

The basic phenomena describing the nuclear magnetic resonance experiment apply equally well to the proton and carbon-13 nuclei. Thus, since the carbon-13 nucleus has a spin of 1/2, it may take up one of the two orientations when placed in a uniform magnetic field.

These are, a lower energy orientation in which the nuclear spin is aligned with the field, and a higher energy orientation in which the spin is opposed to the field (Figure 1). The energy difference between the two states will depend on the magnitude of the applied magnetic field and on the magnitude of the nuclear constants, such as the angular momentum, μ, which is large for carbon-13 compared to that for the proton nucleus. The population of nuclei in each energy state is governed by the Boltzmann distribution (Equation 1).

$$\frac{N_i}{N_j} = e^{-(E_i-E_j)/kT} \qquad (1)$$

Transitions between the energy levels (resonances) can be brought about by absorption of a quantum of electromagnetic radiation in the radiofrequency region. The radiofrequency (rf) required for resonance is given by equation 2.

$$E = h\nu_o = \frac{\gamma h H_o}{2\pi} \qquad (2)$$

$$\nu_o = \frac{\gamma H_o}{2\pi}$$

where γ = gyromagnetic ratio

ν_o = radiofrequency

H_o = applied magnetic field

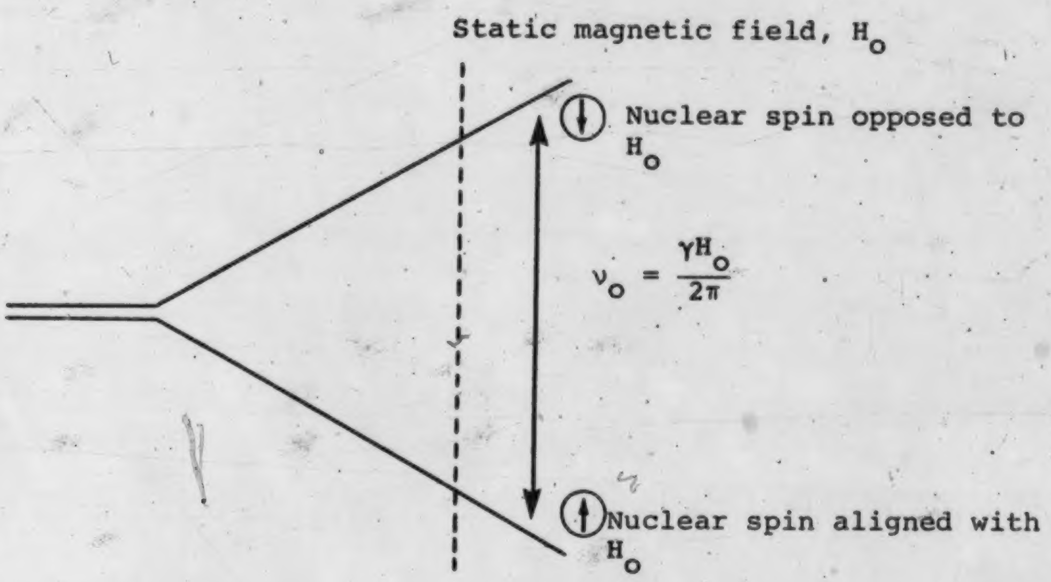

Static magnetic field, H_o
Nuclear spin opposed to H_o
$\nu_o = \frac{\gamma H_o}{2\pi}$
Nuclear spin aligned with H_o

FIGURE 1. Zeeman Splitting of Nuclear Energy Levels in a Magnetic Field.

h = Planck's constant

Carbon-13 nuclei resonate at 22.62 MHz when placed in a magnetic field of 21 kilogauss while protons resonate at 90 MHz at the same field.

The low natural abundance of the ^{13}C isotope (1.1% contrasted to 99.8% for the ^{1}H isotope) and its low nuclear sensitivity (1.6% of that for equivalent number of proton nuclei under similar field) make cmr resonances six thousand times more difficult to obtain than pmr resonances. A brief survey of the historical development in techniques and instrumentation gives a better understanding of how such sensitivity problems have been overcome, thus allowing cmr to emerge to its present status - a powerful analytical tool for structural investigation of organic molecules.

Carbon-13 nuclear magnetic resonance spectroscopy can be considered more generally useful than pmr in organic chemistry studies for two principal reasons. First, cmr gives direct observation of the carbon skeleton for physical property studies, direct observation of sites for carbon reaction and direct observation of functional groups without directly bonded protons, such as carbonyls and nitriles. Second, the cmr spectra are easier to interpret as the carbon-13 resonances of organic compounds are found over a range of ~250 ppm while those of pmr are limited to ~10 ppm for diamagnetic samples. Thus, cmr is particularly useful in the identification of more complex molecules of molecular weight of 300 to 500.

The early cmr experiments [6-8] were conventional continuous wave (cw) nmr and involved either field or frequency sweep; the chemical shifts were obtained by the adiabatic rapid passage technique using relative low magnetic field (10=14 kilogauss), large sample tubes (13-15 mm. o.d.), neat, non-spinning samples and a single sweep over the region of interest with very high (saturating) rf power under unlocked conditions. This technique gave poor resolution (0.5 to 1.0 ppm), low signal to noise ratio, s/n, and only relatively simple compounds could be investigated due to overlapping of the carbon-13 proton multiplets. In 1962, the INDOR technique [9] (Inter Nuclear DOuble Resonance) was found to give greater sensitivity than direct observation of carbon-13 resonances using the rapid passage method. In the INDOR method the carbon satellites in the proton spectrum are observed while irradiating at the ^{13}C-frequency. This technique is limited by the fact that the non-protonated carbons cannot be observed since long range heteronuclear couplings ($J_{^{13}C\text{-}C\text{-}H}$) are small (generally less than 10 Hz) and easily lost in the base line of the pmr spectrum. The technique has been used most successfully by Olah and co-worker.[10] In 1964, Grant [11] reported that sensitivity and resolution of the cmr spectrum could be improved by sample spinning and proton decoupling; it was pointed out that the protons resonance region could be irradiated while observing the cmr spectrum. Proton decoupling yields a single resonance for each non-equivalent carbon centre, whose intensity is increased by approximately three-fold due to the coalescence of the proton multiplets and the nuclear Overhauser effect (NOE).[12] The nuclear Overhauser effect has its origin from the dipolar relaxation induced between the proton and carbon-13 nuclei on irradiation. On complete saturation of the protons, the Boltzmann distribution is disturbed, the carbon-13 nuclei which depend chiefly on the directly attached protons for spin-lattice relaxation react to the equalization of the proton population by changing their own population and this leads to an equilibrium in which excess nuclei in the lower carbon-13 energy level relative to that required for the Boltzmann distribution. This means that more radio-frequency energy will be absorbed by the carbon-13 nuclei as a larger population is now in the lower energy level. Theoretically it can be shown that the intensity of the carbon-13 resonance will be increased by 2.99 times [12], if the NOE is fully operative. With the advent of field-frequency locks to magnetic resonance spectrometers in the mid 60's [13-14], signal enhancement through the use of repetitive scanning and the time averaging technique became possible.[15] In this method, the digitized spectrum obtained from each scan is co-added. Since the signal intensity increases in a direct proportion of the number of scans (n), while the rate of the noise increases by $\sqrt{n}$, the s/n enhancement is $\sqrt{n}$. This allows lowering the limit of concentration which is necessary in order to obtain a useful cmr spectrum. The lower limit of concentration is governed by the stability, sensitivity and homogeneity of the spectrometer and the observation time. By applying time averaging and proton decoupling, high resolution carbon-13 spectra of various relatively simple compounds containing ^{13}C in natural abundance could be obtained by using conventional spectrometers equipped to operate at the appropriate frequency, for example, in an applied field (H_o) of 23.5 kilogauss, carbon-13 nuclei absorb at 25.1 MHz. The next major improvement was the application of Grant's decoupling technique by using a random noise generator to irradiate and decouple simultaneously all proton resonances. Ernst [16] worked out the theory of the technique which consists of using a noise modulated proton decoupling frequency to give an effective excitation bandwidth covering all proton resonances in the sample. The cmr spectrum obtained from the heteronuclear double irradiation experiment gives a single resonance for all non-equivalent carbon sites, thus it affords chemical shift values and carbon counting.

The sensitivity is increased by the collapse of the ^{13}C-H spin multiplets and also by the NOE when compared to that of proton coupled spectrum.

In order to regain the coupling information destroyed by full proton decoupling, Roberts [17] introduced a single frequency off-resonance decoupling (sfor) technique. In this method, the proton irradiation is kept at a high power level; the frequency is moved approximately 500 Hz away from the proton resonances to be irradiated and the noise modulation is switched off. The cmr spectrum from sfor decoupling shows reduced directly bonded ^{13}C-H couplings (residual couplings) and effective elimination of long range C-H couplings. Thus, the spectrum is greatly simplified relative to that obtained by the adiabatic rapid passage method due to the decrease of spectral overlaps. The loss in sensitivity as compared to the noise modulated proton decoupling (broad band proton decoupling) experiment is small because of some residual Overhauser effects. The multiplicities derived from the residual couplings reveal the number of directly attached hydrogens at specific carbon centres by the n + 1 rule familiar from pmr spectroscopy, that is, singlets, doublets, triplets and quartets are obtained from quaternary (non-protonated), methine (CH), methylene (CH_2) and methyl (CH_3) carbons, respectively. Since the residual or observed J_{C-H} is directly proportional to the true J_{C-H} and the distance between the irradiating frequency and the proton resonance frequency, and inversely proportional to the amplitude of the applied radiofrequency field [16] (these quantities are known or can be determined), it is possible to estimate the J_{C-H} values.[18] It is apparent that carbon resonances can be matched with specific proton resonances.[18] The proton selective spin-decoupling technique, which is valuable to carbon-13 analysis, is achieved by irradiating one set of equivalent proton resonances at low radiofrequency power. This leads to the collapse of the carbon multiplets with which this set of protons is coupled, while other protonated carbons retain some ^{13}C-H couplings.[18] The usefulness of proton selective decoupling relies on two conditions: (1) the pmr signal of the proton under consideration has been identified, and (2) it exists in an isolated part of the spectrum so that the directly bonded carbon-13 resonance of interest will be enhanced on decoupling relative to all other peaks in the molecule. This technique was extensively used in the present work.

The advent of the high resolution pulse Fourier transform (PFT) nmr technique [19-23] has been the most useful advance in spectral accumulation. In this technique the sample is exposed to short pulses of rf energy of sufficient power to excite all carbon-13 nuclei simultaneously. As a response to this simultaneous excitation, all nuclei in the sample will resonate. The resulting 'spectrum' detected by the receiver is in the time domain and provides a pattern described as a free induction decay (FID). Fourier transformation, which is essentially a mathematical operation, is performed on the FID to provide a normal absorption spectrum. By time averaging, a series of FID signals will provide a s/n enhancement of $\sqrt{n}$ as in the cw mode, but the time between successive pulses is much lower than for the cw technique. Theoretically this can lead to an enhancement in s/n up to a 100 fold [22] for a comparable time. In practice, the improvement is approximately ten. It is clear that the PFT technique allows carbon-13 measurements within a short time even on dilute samples of a high molecular weight compound without prior ^{13}C enrichment and it does promote cmr to be a well-accepted and routine analytical instrument for organic molecules.

There are two spectral techniques which are used to idenify quaternary carbons. One is noise off-resonance proton decoupling which gives only non-protonated carbons as sharp singlets.[1] The other method is due to Grant and co-workers [24] who pointed out that quaternary carbons could readily be identified by the comparison of calculated and observed intensities of the spectrum. The theory of this technique is based on the fact that the NOE is inversely proportional to the sixth order of distance between the carbon and neighbouring protons as the dipole-dipole relaxation between these two nuclei bring about the observed NOE, hence the quaternary carbons do not usually show dramatic increases in intensity in proton decoupling experiment because of the geometrical dependence of the Overhauser phenomenon.

C. Methods of Carbon-13 Spectral Assignment

The general procedure for the assignment of a carbon-13 spectrum centres mainly on the information provided by the noise decoupling [16] and single frequency off-resonance decoupling experiments.[17] The spectrum from the former method usually gives an enhanced single peak for each carbon nucleus, very often the relative intensity of the signal shows the number of carbons under a certain peak. In addition, the intensities of quaternary carbon resonances are often less enhanced, this serves as a useful but not unambiguous indication of their assignments. This technique provides the chemical shift values and carbon counting of the molecule under investigation. It is usually possible to make tentative assignments on the basis of the chemical shift values exhibited by these single peaks. At the same time, suitable carbon-13 or deuterium labelling aids the analysis as the carbons which are directly related to these changes will give either enhanced or decreased signals. Moreover, suitable model compounds supply a further basis for making the chemical shift assignments as specific structures usually give characteristic carbon-13 chemical shifts.

Due to the presence of residual couplings and the residual NOE, the sfor decoupled spectrum has in place of a single peak for each carbon a multiplet pattern which reveals the hydrogen substitution pattern of all the carbon sites in the molecule. This classification helps to assign and confirm the chemical shift assignments made formerly due to noise decoupling technique. Sometimes it is impossible to observe all the residual splittings of each carbon in very complex molecules. The carbons still can be classified by the observation that the centre of the triplet arising from a methylene off-resonance decoupled carbon signals remains in the same position as the totally decoupled line and the intensity of the centre of the triplet is somewhat reduced; the quaternary carbon signals also remain as singlets with the same intensity at the same position in both noise and single frequency off-resonance decoupled spectrum while the methyl (quartet) and methine (doublet) of the off-resonance carbon signals show symmetrical splitting about their corresponding signals in the noise decoupled spectrum. As mentioned earlier, sfor decoupling also enables one to calculate the $J_{^{13}C-H}$ values.[16,18] When $\gamma H_2/2\pi >> \Delta f$, the size of the residual coupling J_r is given by:

$$J_r \sim \frac{\Delta f J}{\gamma H_2/2\pi}$$

where Δf is the separation of the proton signal from the applied decoupling frequency in Hz. J is the ^{13}C-H coupling constant and $\gamma H_2/2\pi$ is the decoupling field strength.

Occasionally cmr spectra present shifts of carbons of like substitution pattern and they cannot readily be differentiated by calculation of substitution parameters or chemical shift theory. In such instances the proton selective decoupling technique is particularly useful for spectral assignment provided that a fully analyzed pmr spectrum is available. The carbon-13 spectrum can be assigned by directly relating each carbon-13 sharp decoupled singlet with an assigned proton resonance position through selective spin decoupling. This is achieved by employing the decoupling frequency which corresponds to the centre of the multiplets of the proton(s) directly bonded to the carbon-13 nucleus to be assigned.[18] If the pmr signal of the proton under consideration exists in an isolated part of the spectrum, only the carbon-13 peak from the directly bonded hydrogen(s) will maximize relative to all the other peaks in the molecule, an unambiguous assignment for the carbon site can be made. The other peaks in the carbon-13 spectrum may be assigned by the same way by successively stepping the proton decoupling frequency through the known proton spectrum. As pointed out earlier, the method has little use for non-protonated carbons which only show slight enhancement if the long range couplings are eliminated. The latter feature can cause ambiguity in assignment on occasions unless care is observed. Using geometrical arguments [24], which have been discussed earlier, the NOE can be used to assign quaternary carbons based on the prediction of the relative intensities of proton decoupled resonances.[25,26] Conversely, the selective decoupling method can be used for the assignment of complex proton spectra provided that suitable model systems are accessible to give an unambiguous assignment of the carbon-13 spectra, for example, the carbon-13 and proton spectral analysis of acepleiadylene [27] and dihydrostrychnine described in Chapter IV.

The rare earth paramagnetic shift agents, which have achieved wide use in pmr spectroscopy, have been applied in cmr and used in the analysis of the carbon-13 spectra of borneol [28] and some Rauwolfia alkaloids,[29] but have not been used in the present work.

D. Chemical Shifts

The theoretical treatment of carbon-13 shifts has been attempted using several methods [25,27,30-35] including the LCAO-MO (Linear Combination of Atomic Orbitals - Molecular Orbitals), VB (Valence Bond), CNDO/2-SCFMO (Complete Neglect of Differential Overlap - Self-Consistent Field Molecular Orbital), HMO (Hückel Molecular Orbital), and Hartree-Fock perturbation methods. These approaches have been based on the Pople-Karplus formalism [33] which in turn is derived from the Ramsey equation.[36] These theoretical calculations have not been totally successful but do offer some semiquantitative suggestions to predict and rationalize the causation of various shifts. The screening constant can be divided into three terms:

$$\sigma = \sigma_d + \sigma_p + \sigma'$$

where σ_d is a diamagnetic term due to the circulation of the local electrons induced by the applied field about the nucleus of interest. The value of σ_d is determined by the diamagnetic screening term of the well known Lamb formula [37] and is identical to the first term of Ramsey's equation:

$$\sigma_d = \frac{e^2}{3mc^2}\sum_i \langle r_i^{-1}\rangle$$

where $\langle r_i^{-1} \rangle$ is the mean inverse distance of the electron from the nucleus and the expression covers all electrons on the nucleus under investigation. Yonezawa and coworkers [38] calculated the contribution of σ_d in the carbon-13 chemical shifts of alkanes. The value obtained is less than 5 ppm or about one eighth of the total range (~40 ppm) exhibited by the lower saturated hydrocarbons. Spiesecke and Schneider [39] found that the carbon-13 shieldings of monocyclic aromatic systems are dominated by the π-electron densities, the relationship is ~160 ppm/π-electron. Evidently, σ_d (which is governed by the electron density) does not play a very significant part in the carbon-13 shieldings.

σ' is the neighbour-atom term which includes shielding contribution from all other atoms and electrons in the molecule, such as anisotropy in the magnetic susceptibility of neighbouring atoms and ring current effects. This term bears insignificant importance as it only contributes a few ppm to the carbon-shieldings.[25,40-41] Conversely, the dominant factor governing carbon-13 shielding is σ_p, the local paramagnetic term, which can be expressed as:

$$\sigma_p = -\frac{e^2 h^2}{2m^2 C^2 \Delta E} \langle r^{-3} \rangle_{2P} \sum_B Q_{AB}$$

where ΔE is the mean electronic excitation energy, $\langle r^{-3} \rangle_{2p}$

is the 2p atomic orbital dimensions and the term $\sum_B Q_{AB}$ denotes the charge density and bond order matrix in the MO description of the unperturbed molecule.

Based on the studies of various neutral organic compounds, some generalizations on C-13 chemical shifts may be listed as:-

(1) In hydrocarbons the shieldings are affected significantly by hybridization with sp^3 carbons at high field, sp carbons (with the exceptions of central carbons of allenic structures) at intermediate field and sp^2 carbons at lower field. A mark upfield shift (~-2.6 ppm) is found for cyclopropane relative to other alicyclic rings.

(2) Carbon atoms attached to electronegative atoms absorb at low field and the deshieldings are proportional to the electronegativities of the substituents.

(3) Carbonyl carbons are appreciably deshielded relative to olefinic carbons.

(4) Carbons which are involved in steric congestion, in general, are shielded as compared with those which are not.

(5) Carbon-13 shieldings tend to follow additivity

relationships in related series. Thus, it is possible to estimate the shieldings for many compounds with remarkable precision.

(6) Multiple substitution of a carbon nucleus by heavy atoms like iodine cause upfield shifts of the carbon resonance.

(7) When an sp^3, sp^2 or sp carbon is attached to different atoms like carbon, nitrogen or oxygen, the carbon shift is most upfield in C=C, most downfield in C=O and intermediate in C=N compounds.

The shielding ranges exhibited by carbon nuclei in a large variety of neutral organic molecules are shown in Figure 2.

To date a huge collection of carbon-13 chemical shift values of a large variety of compounds have been determined and the shielding effect of an assortment of substituents [42-51], for example, CH_3, OH, OCH_3, COOH, NH, $\overset{+}{NH_2}$, $\overset{O}{\overset{\|}{C}}-OCH_3$ and C=O in aliphatic, aromatic and alicyclic hydrocarbons and heterocycles have been characterized. One of the most useful findings is that carbon-13 shieldings in related series tend to follow additive relationships. Frequently the additive parameters derived for a certain substituent from a group of similar compounds can be applied to correlate the chemical shifts

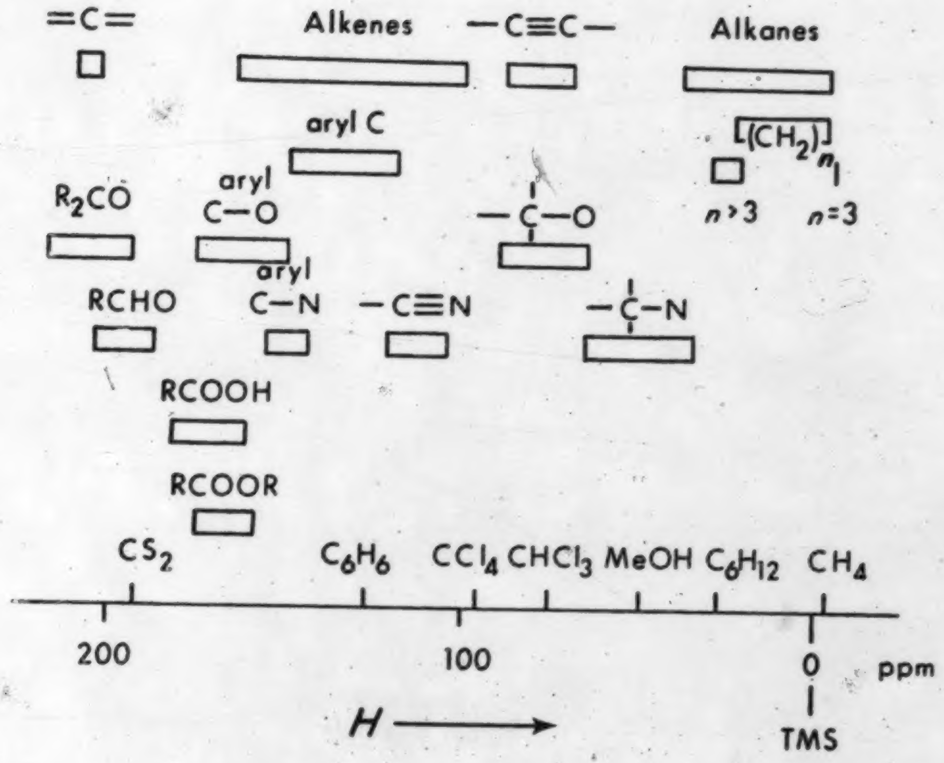
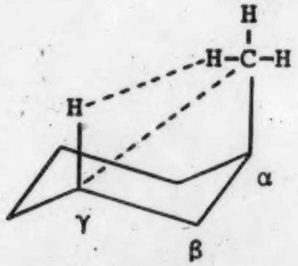


FIGURE 2. Range of ^{13}C Chemical Shifts in Neutral Organic Molecules

of other molecules with the same substituent with remarkable precision. Carbon-13 chemical shieldings are more sensitive to molecular geometry than those of the proton. Often pronounced or measurable differences due to stereochemistry are generally restricted to relatively few proton nuclei in a given molecule, whereas for the same molecule the shielding of several carbons may depend markedly on their orientations with respect to substituents. Thus, cmr is more generally useful for conformational studies.

Based on their work on alkanes, Paul and Grant[52] derived a set of additive shift parameters for shielding calculations of saturated hydrocarbons and proposed that carbons in sterically congested environments tend to absorb at higher fields than those which are not sterically crowded. For example, the shielding γ-effect in butane is due to the nonbonded interactions between the two methyl groups in the gauche rotamer. The relatively close separation of the methyl hydrogen in the gauche form leads to the sterically induced polarization of the terminal C-H bonds such that the electron density at the terminal carbon is increased, thereby causing the observed upfield shift. The stereochemical dependence of the γ-effect is apparent again in the chair conformer of methylcyclohexane[42], that is, the axial methyl group at C-1 shields C-3 and C-5 by 5.4 ppm while an equatorial methyl has little effect on these carbon sites. The observation can again be correlated by the same argument that C-3 and 5 are gauche with respect to the axial methyl group. It is postulated [30,31] that the steric perturbation resulting from the interaction of gauche 1,4-carbon atoms and the proximate proton atoms can induce charge polarization down a ^{13}C-H bond and therefore give the upfield γ-shift in methylcyclohexane. The β-effect of an axial methyl sub-substituent in cyclohexane is observed to be more shielding



than that due to an equatorial methyl, this may be interpreted by the fact that the axial substituent sterically elongates the ring $C_{\beta} - C_{\gamma}$ bond, the $<r^{-3}>$ term of the paramagnetic term is decreased, thereby, causing the β-carbon to move upfield. Similar findings have been obtained from the cmr studies of nitrogen and oxygen heterocycles.[4,45,53,54] The fundamental substituent and additivity parameters obtained show similarity to those noted in cyclohexane [42], though some of the values are attenuated, yet these parameters have proven to be valuable in the analysis of more complex alkaloids.[1-5]

II. Carbon-13 NMR Analysis of Selected Mono and Bicyclic Nitrogen Compounds

A. Introduction

The cmr analysis of the series of nitrogen heterocyclic compounds under present consideration was carried out for four purposes. 1. To determine the substituent effects on the C-13 chemical shifts in 3- to 9-membered rings, in particular, when a CH_2 group is replaced by NH. Hence, the inductive effects of the electronegative nitrogen on the ring carbon shieldings can be investigated in regard to the ring size and strain. 2. To determine whether the substituent effects observed in the methylcyclohexanes [12], which have also been applied with some success to the piperidines [4], are generally valid for heterocyclic systems. 3. To determine the effects of substituents in various derivatives related to the nitrogen atom, such as N-oxides, hydrochloride salts, methylated and methiodated compounds. The generality of these effects was considered valuable in the cmr analysis of the indole alkaloids to be described in Chapter III and IV. Finally, 4. to demonstrate that the cmr technique can be a useful tool in studying molecular conformations by correlating the above empirical relationships with observed chemical shift data.

B. Experimental

Carbon-13 nmr spectra were determined using either a Varian Associates HA-100D-15 spectrometer operating at 25.14 MHz or a Bruker HFX-90 spectrometer in the Fourier mode at 22.63 MHz. The former instrument has a 15 inch magnet interfaced to a Digilab FT/NMR-3 Data System, and associated pulser and proton decoupler. The Data System consists of a Nova 1200 with 4K of core memory and a Data General 128K interactive disc for program or data storage. Field/frequency stabilization is accomplished by the deuterium resonance from the solvent of the sample. Typical experimental conditions involved accumulation of 2000 transients for 0.5 M solutions in 10 mm tubes and a delay of 0.8 sec between pulses with a pulse angle of 20 μs which corresponded to a 30° flip angle. The Bruker spectrometer was used in conjunction with a Nicolet-1085, 20K memory, computer. The instrument consists of a deuterium lock system, a BSV-2 random noise (800 Hz band-width) proton decoupler, and a BSV-2 pulse generator-amplifier. All samples were contained in precision ground 10 mm, o.d. tubes. The spectrometer was used in the cross coil configuration. On average, a 30 μs pulse, corresponding to an approximate tilt angle of 20°, was employed. The delay between pulses was 1.2 sec for the average spectral width of 2500 Hz. Accumulation time averaged 30 mins over 8K data points for concentrations of the order of 0.27 M. For off resonance or coupled spectra this time was doubled.

The pmr spectra were recorded using Varian Associates 60 or HA-100 spectrometers.

Pyrrolidine, piperidine and 3-azabicyclo[3.2.2]nonane were obtained from commercial sources and were purified by either redistillation or recrystallization for spectral determination. Hexamethylenimine, heptamethylenimine, octamethylenimine, 2-methylhexamethylenimine, 4-methylhexamethylenimine and 4-t-butylhexamethylenimine were prepared by the procedure of Blicke and Doorenbos.[55] 2-Methylhexamethylenimine was separated from its isomer (3-methylhexamethylenimine) by column chromatography using aluminum oxide as adsorbant and chloroform as eluting solvent. Ethylenimine was synthesized by a standard method.[56] Azetidine and 2-methylaziridine were prepared according to the procedure of Searles and coworkers.[57] Methylated heterocycles were prepared by the action of formaldehyde on the free amines.[58] The boiling points of the NH and methylated compounds are summarized, along with their corresponding literature values (if available), in Table 1.

The methiodides were obtained by adding equal molar quantities of methyl iodide to the methylated heterocycles in chloroform. The salts were recrystallized from hot methanol. The hydrochloride salts of the free amines and methylated amines were prepared by bubbling

TABLE 1

Experimental Boiling Points of Some N-heterocycles

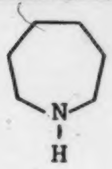
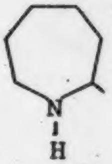
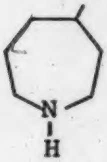
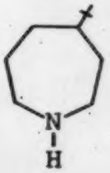
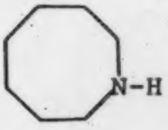
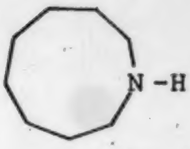
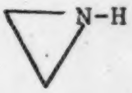
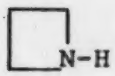
Compound	B. Pt.
	138-131°C (lit. 136-137°C[55])
	145-146° (lit., 148-150°747 mm[55])
	153-154° (lit., 153-156°/748 mm[55])
	79-80°/10 mm
	52-53°/14 mm (lit., 50-67°/17 mm[55])
	63-66°/6 mm (lit., 71-74°/11 mm[55])
	53.5-56.5° (lit., 56-58°[56])
	60-62° (lit., 62.5°/747 mm[57])

TABLE 1 (continued)

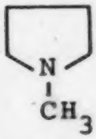
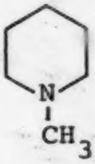
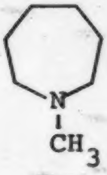
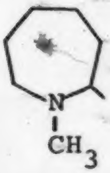
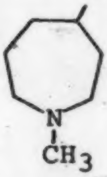
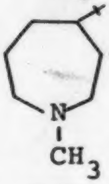
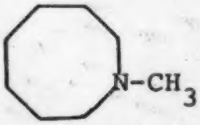
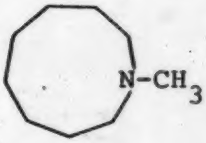
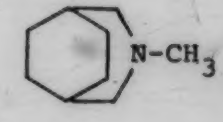
Compound	B. pt.
	76-79° (lit., 80-81° [90])
	49-52°/116 (lit., 105.5° [91])
	69-70°/69 mm (lit., 138-140° [92])
	41-42°/5 mm (lit. 80-90°/50 mm [93])
	51-56°/21 mm (see Appendix)
	76.5-77.5°/3 mm (see Appendix)
	43-45°/10 mm (lit., 144-146°/760 mm [60])
	77-78°/20 mm (lit., 179-181°/746 mm [92])

TABLE 1 (continued)

Compound	B. pt.
	57-58°/2 mm (see Appendix)

dry hydrogen chloride in an ethereal solution of the base; the resulting precipitates were recrystallized to constant melting points from appropriate solvents. The melting points of these salts are listed in Table 2. The N-oxides were synthesized using the procedure of Craig and Parushothaman.[59] These derivatives were characterized spectroscopically by their pmr spectra.

The cmr spectra of the 3- and 4-membered ring compounds were run as neat liquids using acetone-d_6 with an external lock and tetramethylsilane as the external reference. Some methiodides were run as saturated solutions in deuterium oxide using the same external reference. A correction factor of -0.32 ppm was applied to bring these results in line with those where internal TMS was employed. The spectra of the remaining compounds were determined in deuteriochloroform solution with TMS as an internal reference. Deuterium oxide was chosen as the solvent for some methiodated molecules in order to meet concentration requirements for obtaining useful cmr spectral data.

TABLE 2

Experimental Melting Points of Some N-heterocycle Derivatives

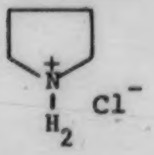
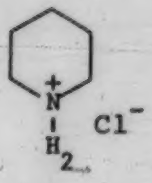
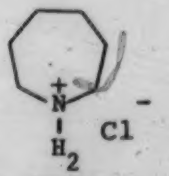
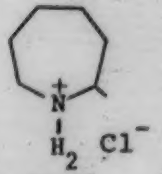
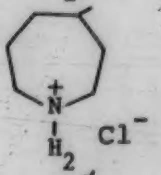
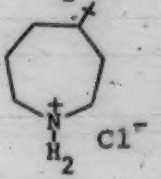
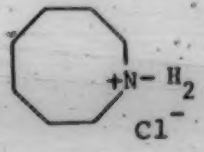
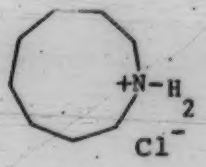
Compound	M. Pt.
	147-140°C
	245-247°C (lit., 246-247°C [94])
	200-203°C
	195-200°C (lit., 202-203°C [55])
	173-174°C (19t., 174-174°C [95])
	216-218°C
	175-178°C (lit., 176-177°C [55])
	160-162°C (lit., 163-164°C [55])

TABLE 2 (continued)

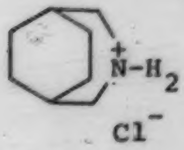
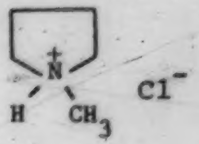
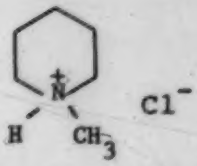
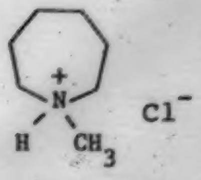
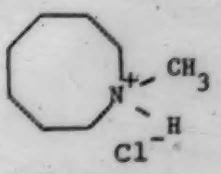
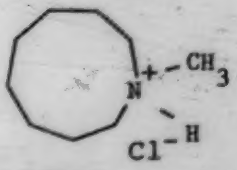
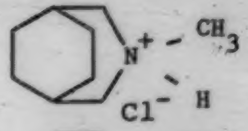
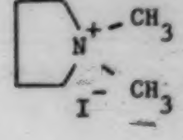
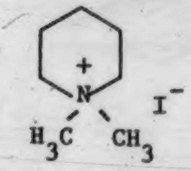
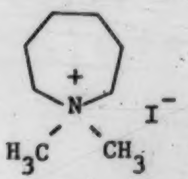
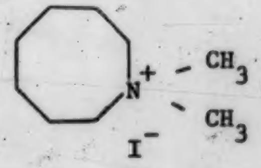
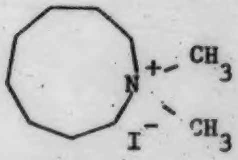
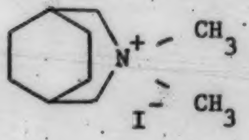
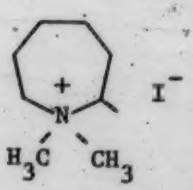
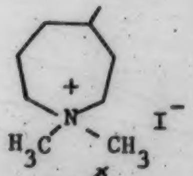
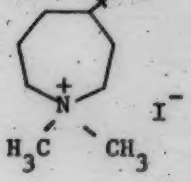
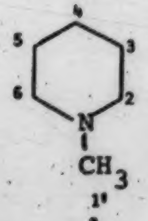
Compound	M. pt.
	287-295°C (sublimation)
	168-170°C (hyposcopic)
	looses its crystalline form at 130-135°; m.p. 205-207°C (lit., 210°C [94])
	180-181°C (lit., 162-163.5°C [93])
	159-164°C (lit., 162-163.5°C [93])
	very hyposcopic
	258-260°C (sublimation)
	>315°C

TABLE 2 (continued)

Compound	M.pt.
	>305°C
	300-302°C
	257-260°C
	258-260°C
	275-280°C
	275-276°C
	180-183°C (lit., 186-188°C[95])
	236-237°C

C. General Aspects of Spectral Assignments

Partial cmr analysis of virtually all the compounds to be discussed was achieved initially by observation of peak intensity and multiplicities determined from sfor decoupling. For example, in 1-methylpiperidine (1), C-2 and 6 are equivalent and so are C-3 and 5. Consequently

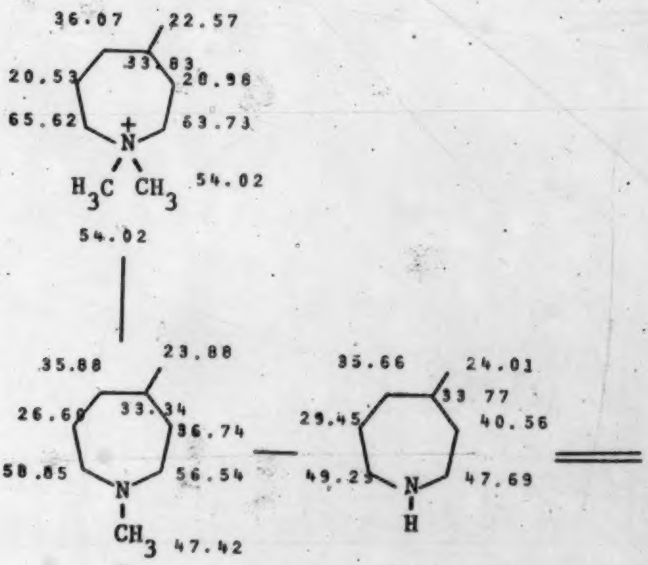


1

their resonances are double the intensity of those for C-4 and C-1'. One of the two double intensity peaks is about 30 ppm downfield from the other. The deshielding inductive effect of nitrogen atom has been established,[61-62,4,45] therefore, the downfield resonance can be assigned to C-2 and 6. The other double intensity peak which shows a similar chemical shift value to the corresponding ^{13}C chemical shifts in methylcyclohexane[42] must be assigned to the β-carbons, C-3 and 5. In addition, the methyl carbon C-1', can be distinguished from C-4 by examination of the sfor spectrum.

When the methyl substituent effects are studied, the α_e-effect is defined as the change in the chemical shift of the α-carbon when its hydrogen is replaced by an equatorial methyl group. In the present work, the α-carbon is replaced by a nitrogen atom and, consequently, the subsequent additivity effects must be considered. The β_e-effect is defined as the change induced in the β-carbon when a hydrogen is replaced by an equatorial methyl group. In this series of heterocycles, it implies that the hydrogen on the nitrogen atom is replaced by a methyl group. The α_a, β_a, γ_a, γ_e, δ_a, δ_e and etc. are similarly defined. These terms are also applied to hydrogen chloride salts, N-oxides and methiodides in which the lone pair of nitrogen is replaced by a substituent.

Comparisons of the C-13 shieldings of the parent compounds and their derivatives show significant differences. Fortunately, a specific carbon is observed to resonate within a precise spectral region. Thus, the carbon chemical shifts can be assigned by comparing the resonance of the derivative with that of the parent. For example, the N-methylation effect on 4-methylhexamethylenimine was determined by subtracting the chemical shift of each carbon of the free amine from that of the corresponding carbon in the methylated product. As a demonstration, the determination of methylation and methiodation effects in 1,4-dimethylhexamethylenimine is shown in Figure 3.

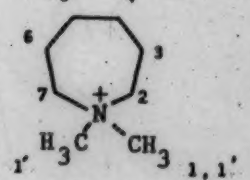


C-2	+8.85	β
C-3	-3.82	γ
C-4	-0.43	δ
C-5	-0.22	δ
C-6	-2.85	γ
C-7	+9.56	β
C-4'	0.13	ε

C-2	+7.19	β
C-3	-7.76	γ
C-4	+0.49	δ
C-5	+0.19	δ
C-6	-6.07	γ
C-7	+6.77	β
C-1'	+6.60	β'
C-4'	-1.31	ε

FIGURE 3. Determination of Methylation and Methiodation Effects in 1,4-Dimethylhexamethylenimine.[a]

a. The numbering system in these molecules:



D. Results and Discussion

1. The Effects of Replacing a CH_2 by NH in Saturated Cyclic Systems

The carbon-13 chemical shifts of selected cycloalkanes and their corresponding nitrogen heterocyclic systems are listed in Table 3. The effect of replacing a CH_2 by NH in these molecules are summarized in Table 4. The observed chemical shifts indicate that the heterocyclic systems are symmetrical at room temperature. At this point we assume that the cycloalkanes and the corresponding heterocycles have the same stable conformation for 7-, 8- and 9-membered rings. These assumed stable conformations are shown in Figure 4 with the nitrogen in position 1. Analogous to piperidine [63], the lone pair of electrons of nitrogen in the boat-chair form of heptamethylenimine is regarded as equatorially oriented, while the nitrogen atoms in the stable conformers of hexamethylenimine and octamethylenimine are considered as axis atoms (atom lying on a twofold axis of symmetry) whose substituents are neither axial nor equatorial, but designated as 'isoclinal'.[64] The proper assignments of the medium size rings were achieved merely by correlation with the inductive effect of nitrogen.

In both the cycloalkane and heterocyclic series, the most shielded carbons are those of the 3-membered

TABLE 3

Carbon-13 Chemical Shifts of Some Cycloalkanes[a] and Nitrogen Heterocycles [b,c]

Compound	Carbon position C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
cyclopropane	-2.60							
ethylenimine	17.76	17.76						
cyclobutane	23.30							
azetidine	49.36	23.31	49.36					
cyclopentane	26.50							
pyrrolidine	47.31	25.89	25.89	47.31				
cyclohexane	27.80							
piperidine	47.69	27.46	25.46	27.46	47.69			
cycloheptane	29.00							
hexamethylenimine	49.67	31.61	27.30	27.30	31.61	49.67		
cyclooctane	27.80							
heptamethylenimine	48.88	29.62	28.48	25.35	28.48	29.62	48.88	
cyclononane	27.00							
octamethylenimine	48.87	28.88	26.94	25.48	25.48	26.94	28.88	48.87

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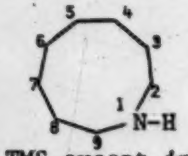
a. See references 50 and 62.

b. The numbering system in this series is:



c. Given in parts per million downfield from TMS except in cyclopropane where the minus sign means upfield from TMS.

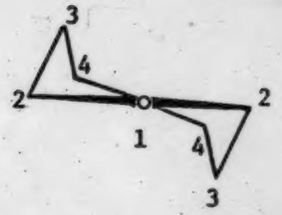
TABLE 4

Effects of Replacing a CH_2 by NH on the C-13 Chemical Shifts of the Heterocycles Listed in Table 3[a]

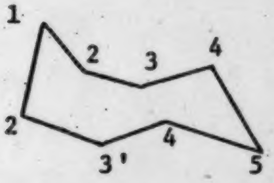
	Effect			
Compound	α	β	γ	δ
ethylenimine	+20.36			
azetidine	+26.06	+0.01		
pyrrolidine	+20.81	-0.61		
piperidine	+19.89	-0.34	-2.34	
hexamethylenimine	+20.67	+2.61	-1.70	
heptamethylenimine	+21.08	+1.82	+0.68	-2.45
octamethylenimine	+21.87	+1.88	-0.56	-1.52

---

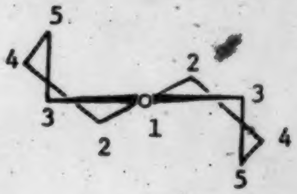
a. Given in parts per million. Negative sign means shielding effect and postive sign means deshielding effect.



Hexamethylenimine in twist-chair form



Heptamethylenimine in boat-chair form



Octamethylenimine in twist-boat-chair form (D_3)

FIGURE 4. Assumed Stable Conformation of 7-, 8- and 9-membered Heterocycles.

rings. There is a difference of approximately 30 ppm between the shielding of the α-carbon in these rings when compared with that in the corresponding 7-membered ring. Macial and Savitsky [62], in their cmr studies of small oxygen, sulphur and N-methylated heterocycles, have suggested that these differences are due to the combined effects of ring strain and ring currents in the 3-membered ring. Both α- and β-carbons generally are deshielded with the increase in ring size up to 7-membered, then the tendency is reversed in the 8- and 9-membered heterocycles. In cyclobutane, the α-carbons are more shielded than those of cyclopentane, but the opposite phenomenon is observed in the heterocycles, hence the most deshielding α-effect (+26.06 ppm) is exhibited in azetidine. The α-effect of the NH group in the heterocycles is quite consistent and gives an averaged value of +20.78 ppm (azetidine is not included in this calculation), this shows that the effect is mainly inductive.

2. N-methylation Effects

The experimental carbon-13 chemical shifts of the N-methylated heterocycles are given in Table 5 and the relative substituent effects are given in Table 6.

From studies in simple piperidines, Cochran [4] and Duch [61] have previously suggested that both piperidine

TABLE 5

C-13 Chemical Shifts of some Methylated Heterocycles[a]

	Carbon position								
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1'
1-methylethylenimine[b]	28.70	28.70							-
1-methylazetidine[b]	57.90	17.70	57.90						-
1-methylpyrrolidine	56.40	24.22	24.22	56.40					42.23
1-methylpiperidine	56.69	26.11	23.93	26.11	56.69				46.94
1-methylhexamethylenimine	58.58	28.10	26.89	26.89	28.10	58.58			47.37
1-methylheptamethylenimine	56.30	27.76	26.36	27.76	26.36	27.76	56.30		47.08
1-methyloctamethylenimine	55.57	26.65	23.88	25.92	25.92	23.88	26.65	57.57	45.82

---

a. Substituent groups are indicated by a prime symbol on the number appropriate to the position of substituent.

b. See reference 62.

TABLE 6

N-Methylation Effects on the Carbon-13 Chemical Shifts of the Heterocycles Listed in Table 5

	Effect			
Compound	β	γ	δ	ε
1-methylethylenimine	+10.94			
1-methylazetidine	+ 8.54	-5.61		
1-methylpyrrolidine	+ 9.09	-1.67		
1-methylpiperidine	+ 9.0	-1.35	-1.53	
1-methylhexamethylenimine	+ 8.91	-3.51	-0.41	
1-methylheptamethylenimine	+ 7.42	-1.82	-2.12	+2.41
1-methyloctamethyleniminie	+ 6.70	-2.23	-3.06	+0.44

and cyclohexane systems exhibit similar methyl substituent effects. In general, taking the present studies into consideration, it is clear that N-methylation causes a more deshielding β-effect than C-methylation of cyclohexanes and C-methylation in piperidines.[4,42,61] γ- and δ-effects are more shielding in the case of N-methylation. The methylation parameters derived for both series are shown in Table 7 for comparison.

Morishima [63] has reported that the lone pair prefers the equatorial orientation in the NH compound and the axial orientation in the N-methyl derivative in conformationally flexible piperidines. If this is so, C-3 and 5 in 1-methylpiperidine and methylcyclohexane would be expected to exhibit different γ_e-methyl effects due to the relative axial orientation of the electron lone-pair in the heterocycle in comparison to the axial hydrogen in methylcyclohexane. Our data and reported findings on piperidines [4,61] show that the γ-carbons are shielded by ~1.3 ppm in methylpiperidines when compared with those in methylcyclohexanes. The observed γ_e methyl-effect in nitrogen heterocycles may be either due to the destabilization induced by the steric interaction between the hydrogens of C-3, 5 and nitrogen lone-pair or simply the intrinsic nature of the γ_e-methyl effect in these heterocycles, or possibly the combination of both factors.

TABLE 7

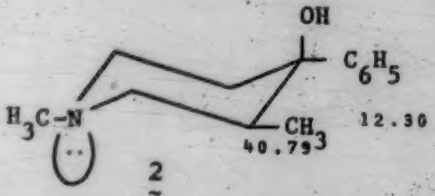
Additivity Parameters of Methylation in Cyclohexanes and Nitrogen Heterocycles

Grant's values of C-methylation in cyclohexanes [42]		Cochran's values of N-methylation in piperidines[4]		Our values of N-methylation in the heterocycles under present considerations	
α_e	$+5.6 \pm 0.2$	β_e	$+9.4 \pm 0.4$	β_e	$+8.66$
β_e	$+8.9 \pm 0.1$	γ_e	-1.2 ± 0.2	γ_e	-2.12[a]
γ_e	0.0 ± 0.6	δ_e	-1.4 ± 0.2	δ_e	-1.78
δ_e	-0.3 ± 0.2			ε_e	$+1.43$
α_a	$+1.1 \pm 0.4$				
β_a	$+5.2 \pm 0.3$				
γ_a	-5.4 ± 0.4				
δ_a	-0.1 ± 0.3				

---

a. The calculation does not include 1-methylazetidine.

In conformationally locked systems, it is apparent that the lone pairs of nitrogen and oxygen cause deshielding effects.[53,54] That is, the chemical shift values of the methyl carbons between (2) and (3), and (4) and (5) show deshielding effects in the case when the methyl group is axially oriented. Thus the γ_e-effect in piperidine and



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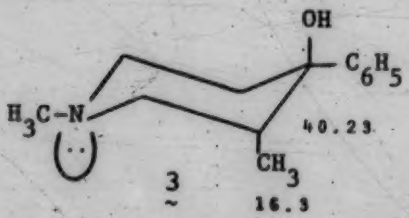

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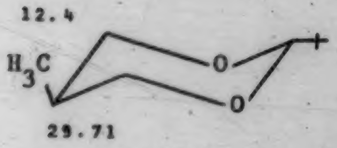

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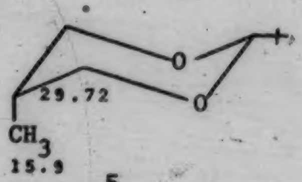

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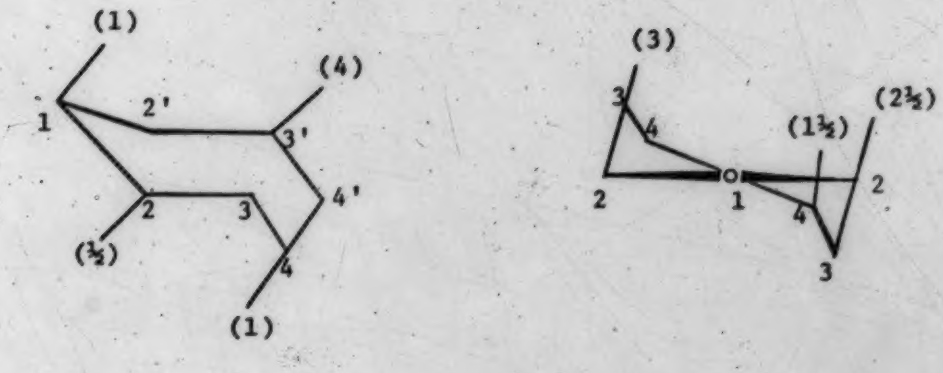
N-methylpiperidine must arise from a balance of shielding and deshielding effects produced by inductive and steric mechanisms. The nature of the lone-pair effect will be further investigated in other heterocycles in this series. Obviously, the more shielding δ-effect of N-methylation in piperidine relative to that obtained in cyclohexane cannot be explained by the steric destabilization due to the electron lone-pair of nitrogen. It is quite evident that methyl perturbation on electronic structures are quite similar in both piperidines and cyclohexanes. By comparing the shift values of N-methylated heterocycles and the corresponding free bases, it is hoped to test if the parameters derived from piperidines can be applied to other heterocycles.

β- and γ-carbons of the N-methylated heterocycles tend to become deshielded with increasing ring sizes up to 7. They then become shielded with increasing ring sizes in 8- and 9-membered rings. The most shielded carbons in this series are the β-carbons in 1-methylazetidine. This compound, therefore, again provides the exception and has the most shielding γ effect of -5.61 ppm. It is probable that this effect in azetidine is due to the ring strain and the bond angle in the molecule, since the substituent cannot introduce the significant steric interaction which would cause such a large effect.

The β-effect has long been a perplexing aspect of C-13 chemical shift additivity. Several attempts[30,43,65] have been made to account for its origin, but no convincing explanation has been put forward. It is interesting to note that the β-effects of various different substituents including the CH_3 group are approximately +10 ppm, the exceptional cases [65,66] are C≡N and COOH, their effects are ~+2 ppm. 'Typical' β-effects as noted in Table 6 are observed in smaller heterocycles even though the α-carbon is replaced by a nitrogen atom. Obviously the introduced CH_3 must have a similar perturbation on the electron environments of the β-carbons (in regard to the substituent) through the nitrogen in these small rings regardless of their different ring sizes, strain and bond angles. The average value of the β-methyl effect in 3- to 7-membered rings is +9.28 ppm. The constancy denotes the additivity relationship of β-parameters within these heterocycles. Hence the less deshielding β-effects in the medium size rings should be attributed to other factors, such as conformational changes, rather than the breakdown of the additivity of this parameter in 8- and 9-membered rings.

For cycloheptane, Hendrickson [64] has calculated that the twist-chair (TC) should be more stable than the chair (C) by 1.4 kcal/mole. The two conformers are shown in Figure 5. The strain energies of the methylcycloalkanes of 7-, 8- and 9-membered rings for all possible substituent positions on each symmetrical conformation were also calculated.[67] It was suggested that the lowest sum of ring energy and substituent energy should appoint the most stable conformations in these systems. Accordingly, the observed carbon-13 chemical shifts of 7-, 8- and 9-membered rings can be used to complement this theory. Even though the most stable conformation of hexamethylenimine has



Heptane in chair-form

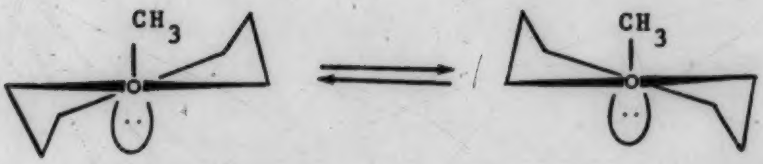
Heptane in twist-chair form

FIGURE 5. Conformers of Heptane.[a]

a (i) see reference 67.

(ii) Values in parentheses give the rough energy of methyl groups place in axial position, taken as the difference of axial values from the average of the equatorial position energies of the ring.

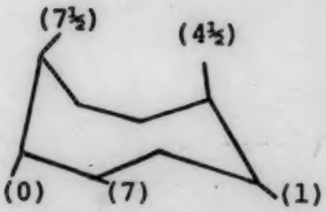
not been determined, it is possible that both cycloheptane and hexamethylenimine have TC as their most stable conformers. When the nitrogen is the axis atom in the C_2 form of hexamethylenimine, the substituents on it, as mentioned earlier, are neither axial nor equatorial, but regarded as 'isoclinal'.[64] The chemical shift data of 1-methylhexamethylenimine gives a shielding γ-effect of 3.51 ppm which is large compared to that in piperidine (-1.35 ppm). The observed value rules out the conformer with isoclinal CH_3 at nitrogen as the major contributor to the observed weighted average carbon-13 spectrum. The two enantiomeric conformer (6) and (7) with isoclinal CH_3 are expected to be in rapid equilibrium and have the CH_3 intermediate in character between axial and equatorial. For either (6) or (7), C-3 and C-6 would have one 'mainly' trans and one 'mainly' gauche methyl interaction. If -1.35 ppm [68] is taken as the effect of an equatorial CH_3 on the C-3 shift and -4.46 ppm [69] as the effect of a corresponding axial CH_3, then the average of -2.91 ppm can be regarded as quite different from the observed value (-3.51 ppm). Furthermore, the observed chemical shift of 47.37 ppm for the methyl substituent indicates that it is free of steric inhibition. Another possible rationalization is that a change of conformation from twist-chair to chair takes place on methylation. In this case, the observed



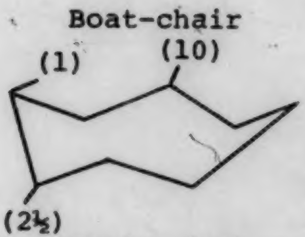
6 7

γ-effect can be correlated to the more severe transannular repulsion between the 'axial' hydrogens of C-3 and C-6 as dictated by the geometry of the molecule when compared to both 1-methylpiperidine and the twist-chair form of 1-methylhexamethylenimine. The δ-carbons are more deshielded when compared with those of 1-methylpiperidine. This finding also supports the view that 1-methylhexamethylenimine exists predominantly in chair-form at room temperature as the hydrogens of C-4 and C-5 are relatively free of steric congestion which was previously found in the twist-chair form of the free amine. Accordingly the chemical shift data strongly suggest that the stable conformer of hexamethylenimine is a twist-chair and that for 1-methylhexamethylenimine is the chair. The change of conformation is most probably brought about by the substituent which has increased the total ring energy in the twist-chair form such that the chair form is the preferred conformer in the methylated compound. This point should be further investigated by energy calculations for these molecules.

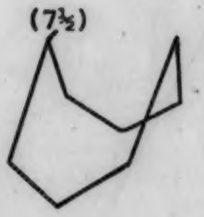
Cyclooctane and its simple derivatives have been shown to exist predominantly in a boat-chair (BC) conformation [64,67] and it has been proved that for rings containing eight or more ring atoms, the conformation of the ring itself appears to be essentially unchanged when a $-CH_2-$ group is replaced by -NH-, -O- or -S- etc.[70] Thus, it is logical to assume that the most stable conformation for heptamethylenimine is a boat-chair. Based on energy calculations, the other two stable conformers of cylooctane are boat-boat (BB) and chair-chair (CC) (Figure 6).[64,67] The BC conformer is more stable than the other two by only 1 to 2 kcal/mole and has Cs symmetry. Transannular repulsions occur between the 'axial' proton at positions 3 and 7 as well as between 1, 4 and 6. If one supposes that the most stable conformer of the methylated derivative is still in BC form with the CH_3 group in the equatorial orientation and extrapolates the shielding effects which are induced sterically by the nitrogen lone-pair (as found previously in the 6- and 7-membered heterocycles) to the boat-chair conformer of 1-methylheptamethylenimine, then one would expect C-4 and 6 to be shielded. Indeed a δ-effect of -2.12 ppm is observed experimentally. However, the β- and γ-carbons also move upfield unexpectedly on methylation. The shielding γ-effect may be rationalized by the



Boat-chair



Chair-chair



Boat-boat

FIGURE 6. Conformers of Cyclooctane[a]

a. See definitions in Figure 5.

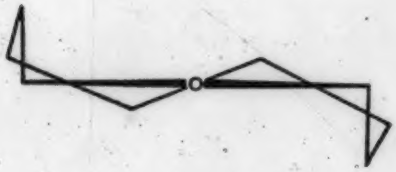
inherent property of methylation of heterocycles, but the shielding of -1.58 ppm shown by the β-carbons when compared to those of 1-methylpiperidine cannot be correlated except by the breakdown of the additivity relationship exhibited by smaller N-methylated heterocycles. Contrary to Lambert [60] who proposed BC as the most stable conformer of 1-methylheptamethylenimine, we speculate that a chair-chair form with the nitrogen lone-pair in an axial orientation is the preferred conformer for 1-methylheptamethylenimine. The steric congestion between the protons of C-2, 4, 6 and 8 can be accounted for the observed less deshielding β- and more shielding γ-effects in comparison with 1-methylpiperidine. The observed γ-effect of -1.82 ppm can be rationalized by the steric interaction between the 'axial' protons of C-3 and 7 and the electron pair of nitrogen. Taking the geometry of the molecule into consideration, the magnitude of the observed effect is comparable to that in 1-methylpiperidine.

Relatively little is known about 9-membered rings. Strain energy [71] and low temperature carbon-13 nmr [72] suggest a conformation of D_3 symmetry, that is, a twist-boat-chair or the [3,3,3] conformation for cyclononane itself. Another conformation which has a different sequence of torsional angle signs has approximately C_2

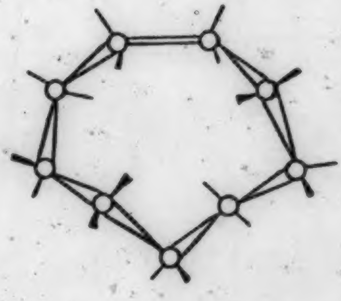
symmetry. The C_2 form (or [1,2,2,2]conformation[73]) is calculated to be 2 to 4 kcal/mole higher in energy than the D_3 form.[71] Both conformers are shown in Figure 7.

Judging from the general upfield shift of all carbon-13 resonances, the 9-membered heterocycles seem to be rather congested. Detailed interpretation of the carbon-13 resonance line positions in octamethylenimine is rather difficult due to the lack of knowledge of the conformations assumed by these substances in the liquid phase at room temperature and the fact that no proton selective decoupling experiments are possible as their corresponding pmr spectra cannot be resolved. The analysis of the carbon-13 resonance lines for the free base is achieved by comparing its chemical shifts with those of its hydrochloride salt and assuming that their stable conformers (two enantiomers which are in rapid equilibrium) are in a D_3 form.

The assignments of the ring carbon resonances of 1-methyloctamethylenimine shown in Table 5 are chosen because of the γ-methylation effects obtained previously. The β-effect involves a shielding of 2.3 ppm as compared to that in piperidine. Both γ- and δ-carbons are shielded by 2.23 and 3.06 ppm, respectively, on methylation. With the supposition that the molecule still retains its D_3 conformation on methylation and using the same argument on the γ-effect of isoclinal CH_3 presented for hexamethyl-



TBC (D_3)



C_2 form

FIGURE 7. Conformers of Cyclononane

enimine, we predict C-3 and 8 to be shielded approximately by 2.91 ppm which is different from the observed shift of -2.23 ppm. It seems logical to call upon a conformational change to explain the observed effects. A conformation of 'modified' C_2 symmetry is proposed. In this conformer, there is more severe transannular repulsion between C-2 and 7 as well as between C-4 9 as compared to those in the D_3 form. The steric congestion that C-5 and 6 have in the D_3 conformer is also relieved in this conformation. This change can explain the observed β-,δ- and ε- effects. In this conformation, either C-3 or 8 (due to rapid equilibrium between the two enantiomers) has 1 gauche CH_3 and 1 gauche electron-pair interaction . The transannular repulsion that C-3 and 8 have in the D_3 conformer is removed in the proposed conformer which will effectively attenuate the expected γ-parameter to the observed value. Moreover, the methyl substituent is found to be slightly shielded relative to that in the 6-, 7- and 8-membered heterocycles. This indicates that the substituent has some steric interaction with the ring carbons as suggested, but the validity of the proposed conformer for 1-methyloctamethylenimine needs further investigation.

3. N-protonation Effects

The chemical shift data determined for the hydrochloride salts of the heterocycles are given in Table 8. The effects of protonation with respect to the corresponding free base are calculated and shown in Table 9. Protonation causes upfield shifts in all ring carbons of the heterocycles. The phenomenon has been rationalized by Morishima [74] who suggested that, on N-protonation, the carbon-hydrogen bond is polarized to the $C^{\ominus}-H^{\oplus}$ form and thus the electron of the hydrogen atom is transmitted to the positively charged nitrogen atom mainly by an inductive effect. The shielding effect of the carbon is caused by the increase in the total charge density on protonation. It seems logical that the same reason is responsible for the upfield C-13 chemical shifts observed in 7-, 8- and 9-membered rings, which have not previously been investigated. There are 3 prominent features of the experimental data, (1) the changes in carbon-13 chemical shifts are large and cover a range of -1.4 to -5.0 ppm, (2) significant effects (ranging from -2.2 to -4.5 ppm) are observed at carbons which are at least three bonds remote from the site of protonation, especially in the 8- and 9-membered rings. This is in sharp contrast to the results of all other substituents, for example, CH_3 which has already been discussed extensively in this chapter, and (3) the carbon atoms in general show an alternating and attenuating charge density buildups, that is, the protonation effects

TABLE 8

Carbon-13 Chemical Shifts of Hydrochloride Salts of Some Heterocycles

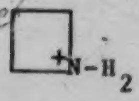
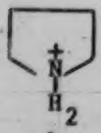
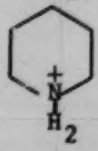
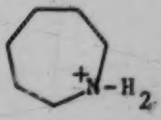
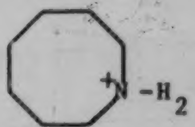
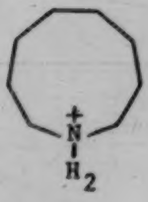
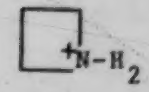
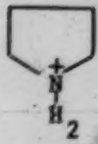
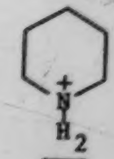
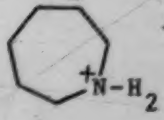
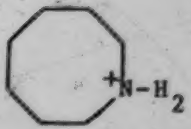
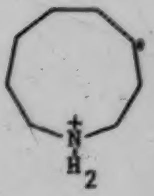
Compound	Carbon position C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
	46.18	18.77	46.18					
	45.21	24.44	24.44	45.21				
	44.67	22.55	22.55	22.55	44.67			
	45.91	26.92	25.09	25.09	26.92	45.91		
	45.14	25.04	23.98	25.04	23.98	25.04	45.14	
	44.97	24.03	23.10	25.34	25.34	23.10	24.03	44.97

TABLE 9

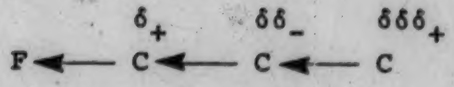
Protonation Effects on the Carbon-13 Chemical Shifts of the Heterocycles Listed in Table 8

		Effect		
Compound	β	γ	δ	ε
	-3.18	-4.54		
	-2.10	-1.45		
	-3.02	-4.91	-2.91	
	-3.76	-4.69	-2.21	
	-3.74	-4.58	-4.50	-0.31
	-3.90	-4.85	-3.84	-0.14

are β < γ, γ > δ and δ > ε.

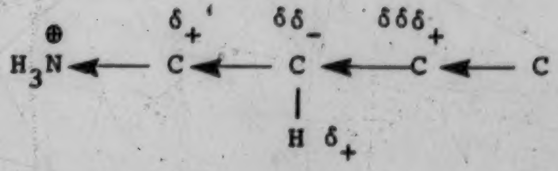
The effects of protonation in piperidines show an additive trend, Duch [61] derived a set of protonation parameters from piperidine and 2-, 3-, 4-methylpiperidine. The values are -2.54 ± 0.26, -4.89 ± 0.50 and -3.51 ppm ± 0.15 ppm for β-, γ- and δ-effect with their respective deviations. The chemical shift parameters obtained for the hydrochloride salts of hexamethylenimine, heptamethylenimine and octamethylenimine follow a similar pattern. This indicates that there is no significant conformational change on protonation but that the effects are most likely electronic in origin. The hydrochloride of pyrrolidine gives the smallest β- and γ-effect in the series.

The features of the carbon-13 chemical shifts exhibited by the protonated species of some cyclic secondary amines have already been interpreted by charge density variations.[74] Our results correspond well with the predictions made by Pople et al. [75] on the σ-inductive effect. Using the CNDO-SCF molecular orbital calculations, Pople [75] proposed that the inductive effect induced by an electronegative substituent alternates and attenuates along the σ skeleton. Consequently, the distribution of the charge densities due to protona-



$$F \longleftarrow \overset{\delta_+}{C} \longleftarrow \overset{\delta\delta_-}{C} \longleftarrow \overset{\delta\delta\delta_+}{C}$$

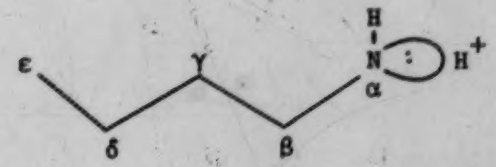
tion can be rationalized schematically as:



$$H_3\overset{\oplus}{N} \longleftarrow \overset{\delta_+}{C} \longleftarrow \underset{\underset{H\ \delta_+}{|}}{\overset{\delta\delta_-}{C}} \longleftarrow \overset{\delta\delta\delta_+}{C} \longleftarrow C$$

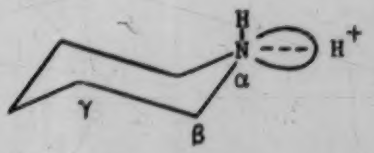
The δ-protonation effect of piperidine observed in the present study is less deshielding than the β-effect. This differs from Morishima et al.[74] who found the β-effect was more shielding than the δ-effect. The difference may be explained by the different acids used for the protonation studies. Hydrochloric acid was employed in the present study while Morishima et al. used trifluoroacetic acid. The present data agree better with Pople's calculations. The attenuating nature breaks down in heptamethylenimine hydrochloride as the β-effect is less shielding than both the γ- and δ-effects. Moreover the inductive effect is largely diminished in carbons which are more remote from the site of protonation since the ε-carbon in heptamethylenimine and octamethylenimine hydrochlorides are only slightly shielded by 0.31 and 0.14 ppm, respectively, upon protonation. This reflects the sensitivity of the σ-inductive effect on the distance from the site of the electronegative substituent.

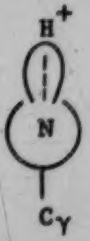
Based on their work on 6-membered heterocycles, Morishima et al. [74] proposed that the protonation parameters are governed by (1) the orientation of the nitrogen lone-pair, that is, either axial or equatorial, and (2) the conformation of the intervening carbon skeleton. The parameters thus depends on the size of the dihedral angle, θ, between the lone pair and the C_β -C_γ bond. The γ-carbons are found to be shielded by about 4.8 ppm when the lone pair is in the equatorial position; that is, when N-protonation occurs through a 'zigzag path' as in the stable conformer of the free amines. Furthermore the



'zigzag path'

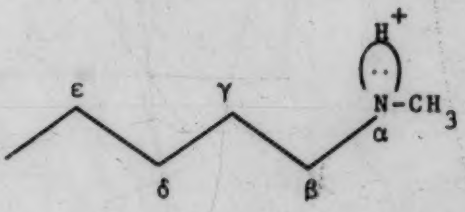
dihedral angle between the lone-pair lobe and C_β - C_γ bond in the same conformation is 180°, the relationship between the size of θ and the magnitude of the γ-protonation effect is substantiated by MO calculations.[74] The lone-pair of nitrogen has been recognized as axially





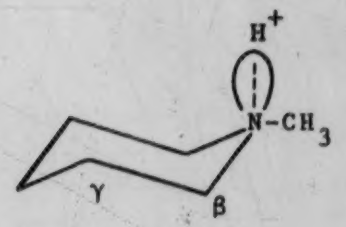
θ = 180°

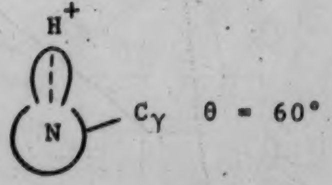
oriented for 1-methylpiperidine [63], the path of protonation is regarded as 'folded'. The γ-protonation effect is



'folded path'

deshielded by approximately 2 ppm relative to that observed in 'zigzag path'. The γ-effect shown by the protonated derivative of 1-methylpiperidine is -2.8 ppm.[74] The dihedral angle in the molecule is 60°.





Theoretical calculations, using the pseudo-atom approach[76], predict the changes in the charge density, upon protonation, in relation to the dihedral angle follow the order ; θ = 0 (cis) > θ = 60° > 180° (trans) > 120° (Figure 8). Hence, the theoretical protonation effect exhibited by the γ-carbons of 1-methylpiperidine hydrochloride would be estimated to be more shielded when compared with that shown by the corresponding carbons of piperidine hydrochloride. However, experimentally,

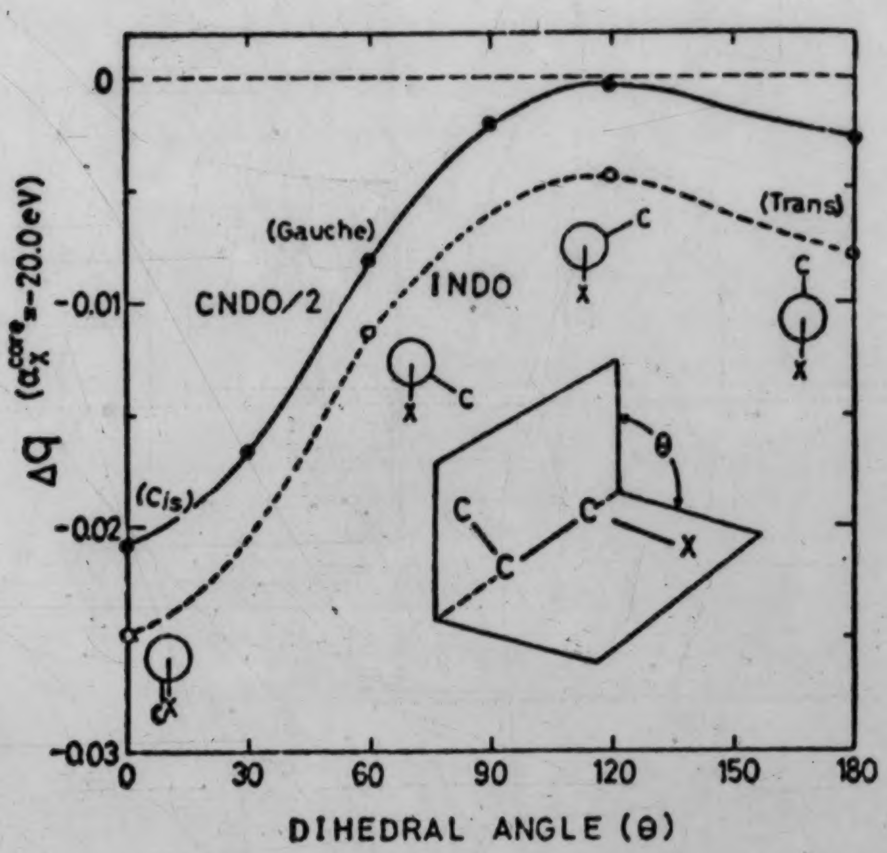
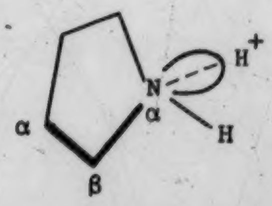
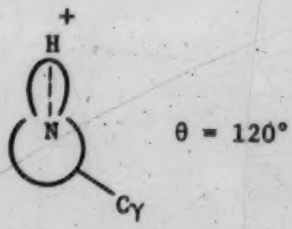
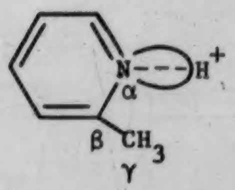


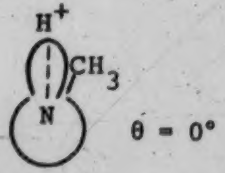
FIGURE 8. Δqc_γ Varying with Dihedral Angle θ^{74}

this is not so. In pyrrolidine hydrochloride when θ is 120°, the γ-protonation effect is -1.45 ppm, while the shielding effect exhibited by the carbons of the protonated species of α-picoline is -5.30 ppm [74], the θ in this compound is 0°. Accordingly, the γ-effects observed for 5- and 6-membered nitrogen heterocyclic protonated molecules fall into the order of θ = 0° (cis) > θ = 180° (trans) > θ = 60° > θ = 120°.

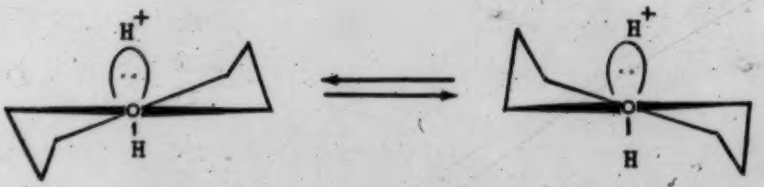








Based on the most stable conformer (BC) of heptamethylenimine, the observed γ-protonation effect of -4.58 ppm seems to fit the 'zigzag path' and 180° dihedral angle trend. However, the experimental γ-effect of -4.69 and -4.85 ppm for the 7- and 9-membered rings, respectively, are similar to that in piperidine hydrochloride, but the stable conformer proposed earlier for hexamethylenimine and octamethylenimine are twist-chair and D_3, respectively, with nitrogen situated in such a position that gives isoclinal substituents in both cases. The dihedral angle will be approximately 60° and 180° due to the rapid equilibrium between the enantiomeric conformers (8) and (9). At the same time, the protonation



8 9

effect will be transmitted through the 'mainly zigzag' and 'mainly folded' mechanisms due to the equilibrium. Evidently, our findings denote that the 'path' and dihedral angle explanation which are based on the behaviour of the 6-membered heterocycles cannot be easily extrapolated to the larger heterocycles. It is pertinent, at this present stage, to formulate the following probable reasons for our observations: (1) The values of the γ-protonation effects in 7- and 9-membered heterocycles correlate better with the theoretical calculations which predicts the change in charge density upon protonation when θ is 60° is slightly greater than that when θ is 180° (Figure 8). Taking the average of the two changes, the observed γ-effects of hexamethylenimine and octamethylenimine hydrochlorides seem to be reasonable in the range of -4.70 to -4.85 ppm. (2) The angular dependence of the protonation effect may not work for nitrogen heterocycles of sizes other than 5- and 6-membered rings. Disregarding the ring size and strain, the γ-effect of -4.86 ppm shown by azetidine hydrochloride cannot be rationalized by the size of θ as the value predicted should be in the range of -1.5 ppm because θ is 120° which is similar to that in pyrrolidine hydrochloride. The difference between the observed and predicted values leads one to question the extent of application of this angular feature found in protonated piperidine to other heterocycles. We conclude that the carbon-13 chemical shifts of the 4-membered heterocyclic ring is dominated by ring strain and size. (3) The relationship between the paths of protonation and the magnitude of the γ-protonation effect cannot be applied to heterocycles whose conformations do not exhibit distinctive 'zigzag' nor 'folded'pathways.

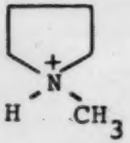
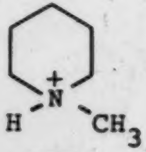
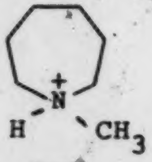
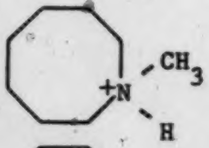
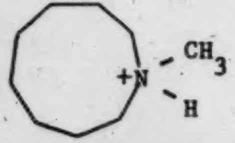
The long range δ- and ε-protonation effects are the most difficult to explain since no steric interaction at these sites is expected and the inductive effects are sharply attenuated beyond the β-position. Calculation of charge densities [61] at C-4 induced by an intramolecular electric field effect associated with a NH polar bond provides a reasonable account of the δ-carbon chemical shift of piperidine hydrochloride. Although it is premature to draw an analogy, without theoretical calculations, between 6-membered and medium size rings in this respect, it is highly probable that the same phenomenon is operative in 7-, 8- and 9-membered rings.

The hydrochloride salts of the methylated nitrogen heterocycles were prepared and their carbon-13 chemical shifts are given in Table 10. The observed protonation effect relative to the corresponding tertiary amines were determined and are listed in Table 11. Protonation has a shielding effect on all carbon atoms. The carbons which are three bonds away from the protonated nitrogen still show relatively large shielding effects. The electric field effects may be the origin of the δ- and ε-shifts in these systems. Comparison of the data in Table 9 and Table 11 shows protonation generates different shielding effects in secondary and tertiary amines.

Some difficulties were encountered in assigning the γ- and δ-carbons in 1-methylhexamethylenimine and 1-methylheptamethylenimine hydrochloride. Jones [45] derived a set of protonation parameters for 1-methyl-4-piperidones, the values were -3.1, -2.8 and -3.7 ppm for the β-, γ- and δ-effect, respectively. The charge distributions induced by protonation in these tertiary amines (in contrast to those observed in secondary amines) is the smallest in the γ-carbons. These additive parameters also correlate with those on the protonated 1-methylpiperidines reported subsequently by Morishima et

TABLE 10

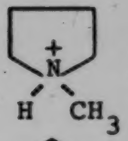
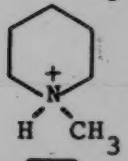
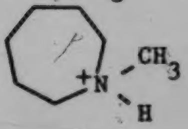
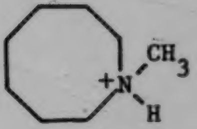
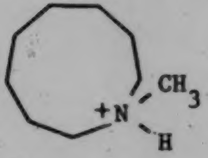
Carbon-13 Chemical Shifts of Hydrochloride Salts of Some Methylated Heterocycles[a]

	Carbon position								
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1'
	55.38	23.78	23.78	55.38					40.92
	54.99	22.96	21.55	22.96	54.99				43.92
	56.86	(26.38)	(23.74)	(26.38)	(23.74)	56.86			44.88
	53.41	(25.68)	(22.66)	24.33	(22.66)	(25.68)	53.41		44.07
	52.87	24.06	22.06	24.60	24.60	22.06	24.06	52.87	43.97

a. Parentheses indicate the assignments of the γ- and δ-carbons are interchangeable within a molecule.

TABLE 11

Protonation Effects on the Carbon-13 Chemical Shifts of the Heterocycles Listed in Table 10

	Effect				
Compound	β	γ	δ	ε	β'
	-1.02	-0.44			-1.28
	-1.70	-3.15	-2.38		-3.02
	-1.72	-1.72 (-4.36)	-3.15 (-0.51)		-2.49
	-2.89	-2.08 (-5.10)	-3.70 (-0.68)	-3.43	-3.01
	-2.70	-2.59	-1.82	-1.32	-1.85

al.[74] who rationalized their experimental data by the 'path' and dihedral angle argument discussed earlier. The favoured conformer of 1-methylhexamethylenimine and 1-methylheptamethylenimine, as reported in the methylation section, are the chair and chair-chair forms, respectively with the lone-pair of nitrogen in an axial orientation. Accordingly, the courses of protonation are folded and the dihedral angles are 60° in both cases, the situation is similar to that found in 1-methylpiperidine. If one extends Jones' protonation parameters [45] and applies the 'folded path' and dihedral angle view derived from the 6-membered heterocycles to the N-methylated 7- and 8-membered ring, the resonance at 26.38 ppm and 25.68 ppm can be assigned to the γ-carbons of 1-methylhexamethylenimine and 1-methylheptamethylenimine hydrochloride, respectively. These assignments subsequently gives -1.72 and -2.08 ppm for the γ-protonation effects for the respective tertiary amines. These values correspond well with those derived from the 6-membered heterocycles. The more shielding γ-effect of -2.59 ppm observed in 1-methyloctamethylenimine hydrochloride can be visualized as the average of the values due to the rapid equilibrium between enantiomers in which the dihedral angle is 60° and 180° and the path can be both 'folded' and 'zigzag'. Conversely, if one only considers the theoretical calculation [74] which predicts the charge distribution to be greater at γ-carbon when θ is 60° than when it is 180°, then the assignments of γ- and δ-carbons should be reversed. Following this analysis produces -4.36 and -5.10 ppm for the γ-protonation parameter in the 7- and 8-membered ring, respectively. The interpretation of the γ-shielding in the 9-membered ring remains invariable. Due to the fact that there are two equally acceptable approaches leading to different analyses, the assignment of the γ- and δ-carbons of 1-methylhexamethylenimine and 1-methylheptamethylenimine hydrochloride are presently interchangeable. The γ-carbon of 1-methylpyrrolidine is shielded by 0.44 ppm upon protonation. This is more attenuated than that observed in the hydrogen chloride of pyrrolidine which also has a dihedral angle of 120°. Both γ-effects, as predicted by theoretical calculations, are small in comparison to those observed at different dihedral angles.

4. Methiodation Effects

Table 12 shows the experimental carbon-13 chemical shift values for quaternization of the heterocycles with methyl iodide (methiodation) and the observed effects of the substituents (both CH_3 and CD_3) are tabulated in Table 13. The quaternization effects were obtained by subtracting the chemical shift of each carbon of the N-methylated compound from the chemical shift of the cor-

TABLE 12

Carbon-13 Chemical Shifts of Some Methiodated Heterocycles

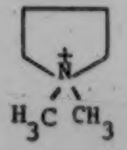
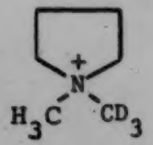
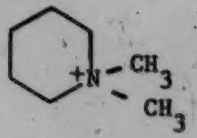
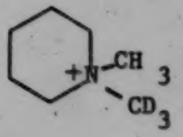
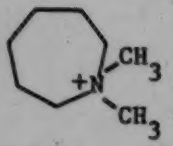
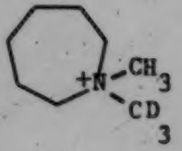
Compound	Carbon position C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1'	C-1-1'
	66.52	22.28	22.28	65.52					52.52	52.52
	66.41	22.28	22.28	66.41					52.60	52.60
	64.60	21.65	21.65	21.65	64.60				53.68	53.68
	63.68	20.63	21.11	20.63	63.38				52.65	52.65
	66.89	22.17	27.46	27.46	22.17	66.86			54.43	54.43
	66.98	22.47	27.62	27.62	22.47	66.98			54.57	54.57

TABLE 12 (continued)

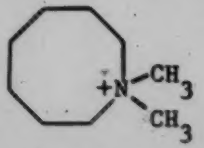
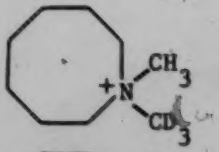
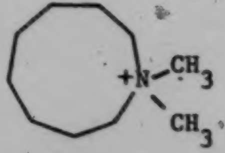
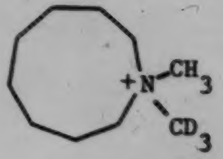
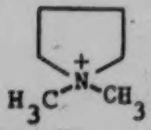
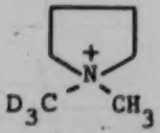
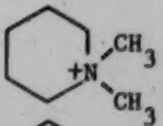
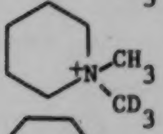
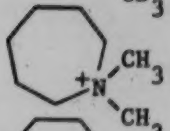
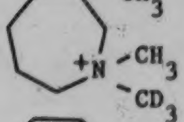
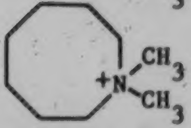
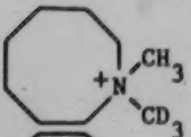
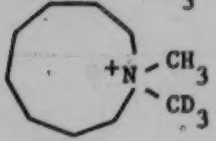
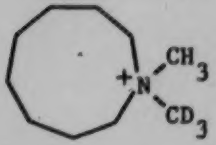
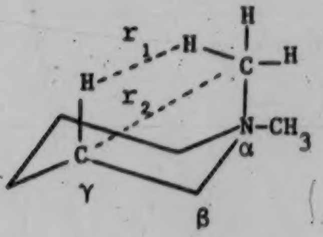
	61.87	22.23	26.36	24.27	26.34	22.23	61.87		53.62	53.62
	61.50	22.27	26.31	24.46	26.31	22.37	61.50		53.88	53.88
	59.40	21.31	18.91	24.85	24.85	18.91	21.31	59.40	52.28	52.28
	59.51	21.84	19.46	25.38	25.38	19.46	21.81	59.51	52.86	52.86

TABLE 13

Methiodation Effects on the Carbon-13 Chemical Shifts of the Heterocycles Listed in Table 12

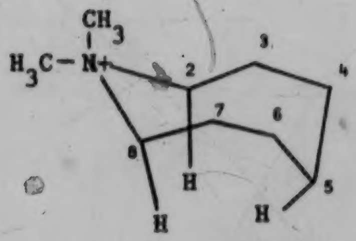
	Effect			
Compound	β	γ	δ	ε
	+10.12	-1.94		
	+10.01	-1.94		
	+ 7.91	-4.46	-2.28	
	+ 6.99	-5.48	-2.82	
	+ 8.31	-5.93	+0.57	
	+ 8.40	-5.63	+0.73	
	+ 5.57	-5.53	0.00	-3.49
	+ 5.20	-5.49	-0.05	-3.30
	+ 3.83	-5.34	-4.97	-1.07
	+ 3.94	-4.81	-4.42	-0.54

responding carbon in the methiodated product. Deuterium oxide was chosen as the solvent for these derivatives in order to meet the concentration requirement for obtaining useful cmr spectral data. In view of the observation that molecular structure contributes significantly to the carbon-13 shieldings when compared with solvent effects in the hydrochlorides of piperidines,[61] it was decided that solvent and concentration effects do not require corrections for the present series of salts of the nitrogen heterocycles. From Table 13 it is apparent that the axial methyl substituent at the nitrogen causes a downfield shift of ~4 to 10 ppm at the β-carbons while most of the other carbons are shielded. The 5-, 6- and 7-membered ring systems exhibit typical β-substituent effects, though the values are quite scattered. The larger rings deviate from the sequence. The observed β-effects are more shielded by 2.34 and 4.08 ppm for 8- and 9-membered rings, respectively, compared to that in piperidine. As these compounds have an axial methyl substituent, the γ-carbons of the ring are expected to be shielded if the ring geometry allows the syn-axial 1,3-steric interaction as shown in (10). Hence, 1,1-dimethylhexamethylenimine and 1,1,-dimethylheptamethyleniimine in their respective stable chair and stable chair-chair conformations are expected to exhibit sig-



10

nificant γ-effects. The observed effects are more shielding than those observed in the 6-membered heterocycles. Since the lengths of r_1 and r_2 in (**10**) are shorter in 7- and 8-membered rings, more severe steric interaction causes the chemical shift of the γ-carbons to move more upfield. However, the β- and ε-chemical shift parameters of 1,1-dimethylheptamethylenimine cause some problems since there are at least two ways to rationalize the observed data. First, the second methyl substituent fails to give the usual additivity relationship at least for the β-carbons in this series. This deduction is made because the value of its β-parameter is attenuated as compared to those of the smaller ring systems in which there are no substantial conformational changes upon methiodation. Second, steric congestion is introduced between C-2, 5 and 8 when the molecule changes from a chair-chair form to a boat-chair which is shown in (**11**). Generally, a methyl group does



Boat-chair

11

not have any inductive effect on carbons which are three bonds away from the site of substitution. Indeed the electric field effect, which has already been introduced in discussions of the protonation effect may provide an explanation of the observed ε-effect as the nitrogen atom in both methiodated and protonated derivatives is being quaternized. If the electric field effect is responsible for the upfield shift of C-5, then C-4 and C-6 are expected to be shielded as observed in piperidine hydrochloride. Experimental data, however, show that these δ-carbons are practically unaffected by methiodation. This strongly suggests that there is a change of conformation to the boat-chair form (11) in the methiodide. The removal of the mild steric congestion between the protons of the β- and δ-carbons in the chair-chair form of the methylated derivative deshields C-4 and C-6 of the methiodide, but the shielding due to the electric field effect, perhaps, paritally negates the downfield shifts.

The observed δ-effect may be rationalized by the combination of these two opposing mechanisms.

In 1,1-dimethyloctamethylenimine, the γ-carbons are shielded by -5.34 ppm on methiodation. This can be explained by the additional CH_3 gauche effect on C-3 and 8, whereas, the observed β-effect is shielded by 4.08 ppm when compared with that obtained in the 6-membered ring system. It seems probable that there is a conformational change in this system since C-4 and 7 also move upfield by 4.65 ppm on methiodation. These shifts are too large to be accounted for by inductive and electric field effects, although the latter is regarded as the causation of the upfield shift of 3.84 ppm of C-4 and 7 in octamethylenimine upon protonation. Probably, steric interaction is induced between C-2, 9, 4 and 7 in methiodation. Alternatively, the non-additive nature of the second methyl substituent may be used to rationalize the observed effects in the 9-membered ring system.

5. N-oxidation Effects

Table 14 summarizes the carbon-13 chemical shift values of the N-oxides of several of the heterocycles studied. The corresponding chemical shift parameters are listed in Table 15. The N-oxidation effects were determined by the same method used for methiodation.

TABLE 14

Carbon-13 Chemical Shifts of N-Oxides of Some Heterocycles

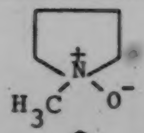
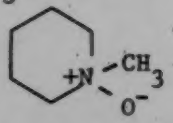
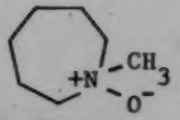
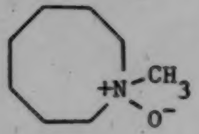
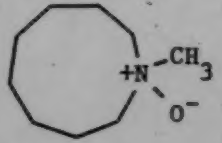
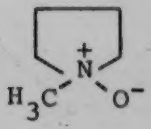
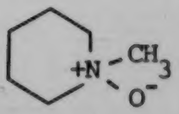
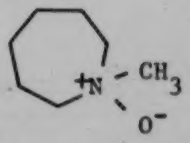
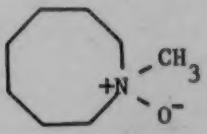
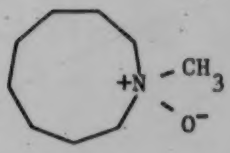
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1'
	Carbon position								
	69.54	22.23	22.23	69.54					56.21
	67.06	21.20	21.71	21.20	67.06				59.72
	71.37	21.85	26.70	26.70	21.85	71.37			60.37
	66.25	22.62	26.55	24.27	26.55	22.62	66.25		58.49
	64.50	23.30	21.40	25.57	25.57	21.40	23.30	64.50	58.05

TABLE 15

N-oxidation Effects on the Carbon-13 Chemical Shifts of the Heterocycles Listed in Table 14

Compound	Effect				
	β	γ	δ	ε	β'
	+13.14	-1.99			+13.98
	+10.37	-4.91	-2.22		+13.78
	+12.79	-6.25	-0.19		13.00
	+ 9.95	-5.14	+0.19	-3.49	+11.41
	+ 8.93	-3.35	-2.48	-0.35	+12.23

From Table 15 it is clear that oxidation is similar to methiodation and causes downfield shifts (9 to 13 ppm) at the β-carbons and upfield shifts at all other sites. In terms of substituent effects, the oxygen generally has a deshielding effect when compared with CH_3 in quaternization. The γ-effect (except in the 5-membered ring) is approximately of the order of magnitude expected for purely a steric interaction with negligible contribution from inductive and electric field effects. On the basis of the chemical shift values of the N-methyl substituents, it can be concluded that the oxygen moiety occupies the axial position in the favoured conformer of these heterocycles. The average oxidation parameters determined for the ring carbons from the present analysis are +11.04, -4.91, -1.18, and -1.92 ppm for β-, γ-, δ and ε-effects respectively. The calculation does not include the γ-shielding of the 5-membered ring. The observed differences in the chemical shift parameters between oxides and methiodides are due to different substituents rather than conformational transformations. Moreover, the oxidation is stereospecific as the amine oxides show only one isomer.

6. Hexamethylenimine Derivatives and Related Compounds

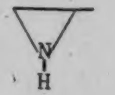
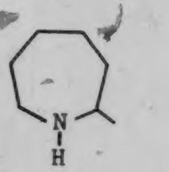
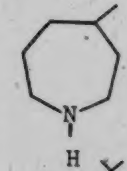
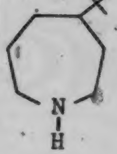
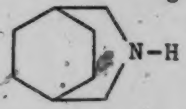
a. C-methylation Effects

The carbon-13 chemical shifts of the substituted hexamethylenimines studied and the related 3-azabicyclo-[3.2.2]nonane are summarized in Table 16, which also shows the C-methylation parameters of these compounds relative to the unsubstituted bases.

Alkyl substitution at either the 2 or 4 position of hexamethylenimine removes the equivalence of C-2, 7, C-3, 6, C-4, 5 and gives additional resonance signals. However, initial assignments were achieved by applying the additivity parameters derived for the C-methylation in the piperidines [4] and 1-methyl-4-piperidones.[45] The substituents were assumed to be "equatorial" in orientation in agreement with the ring energy calçulations for methylcycloalkanes.[67] That is, it is assumed that the conformer with the axial C-methyl group only provides a minor contribution at room temperature. The equatorial methyl group has been shown to produce negligible changes on the shielding of carbons which are three bonds remote from the site of substition, thus the chemical shifts of C-2, and 7 of 4-methyl- and 4-t-butylhexamethylenimine are expected to be similar to the shifts of the corresponding carbons in hexamethylenimine. The shifts of 4-methylhexamethylenimine at 47.69 and 49.29 ppm are assigned to C-2 and C-7, respectively. The chemical shifts of C-5, 6 and 7 of 2-methylhexamethyl-

TABLE 16

Carbon-13 Chemical Shifts of Hexamethylenimines and Their Effects of C-methylation[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Methyl	C-4' (q)
					Carbon Position						
 [b]	- -	24.85 (+6.77)	25.58 (+7.50)							19.24	
	- -	55.02 (+5.33)	38.83 (+7.23)	25.62 (-1.68)	27.30 (0.00)	31.40 (-0.21)	47.69 (-1.98)			24.11	
	- -	47.69 (-1.98)	40.56 (+8.95)	33.77 (+6.47)	35.66 (+8.36)	29.45 (-2.16)	49.29 (-0.42)			24.01	
	- -	48.83 (-0.84)	32.32 (+0.71)	48.63 (+21.33)	28.06 (+0.76)	30.87 (-0.74)	49.60 (-0.07)			27.47	33.54
 [c]	32.91 (+1.30)	55.89 (+6.22)	- -	55.89 (+6.22)	32.91 (+1.30)	25.46 (-1.84)	25.46 (-1.84)	25.46 (-1.84)	25.46 (-1.84)		

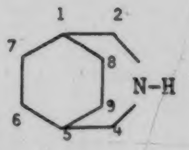
(continued.......)

Footnotes to Table 16

a. Value of the effect shown in parenthesis for the corresponding carbon.

b. Included merely for comparison

c. The numbering of the system



enimine are assigned similarly. Using the α_e-methyl substituent parameter of the piperidines (Table 17), it is predicted that C-2 and C-4 of 2-methylhexamethylenimine and 4-methylhexamethylenimine will move downfield by about 5 to 6 ppm from the corresponding carbons in hexamethylenimine. Thus, the resonances at 55.02 ppm and 33.77 ppm are assigned to the tertiary ring carbons of the 2-methyl and 4-methyl heterocycle, respectively. The assignments were confirmed by the off-resonance method which also defined the assignment of the methine resonances due to C-4 in 4-t-butylhexamethylenimine and C-1 and 5 in 3-azabicyclo[2.2.2]nonane.[a]

In 2-methylhexamethylenimine, the resonance at 38.84 ppm can be assigned to C-3 (calculated to be 39.9 ppm), thus leaving C-4 in this compound to be assigned by difference. The predicted values of 39.91 ppm for C-3 and 35.60 ppm for C-4 in 4-methylhexamethylenimine agree reasonably well with the observed values of 40.56 and 35.66 ppm. This indicates the shifts are properly assigned in this compound. Because of its bulky size, the tertiary butyl group is generally used as a locking group in studying ring conformation since it prefers an equatorial configuration. The substituent effects of this alkyl group have not been well characterized and are found to vary.[44,54] The α_e-effect of this substituent

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[a] Referred to as bicyclic octamethylenimine henceforth.

TABLE 17

Substituent Parameters for C-methylation in 6- and 7-Membered Ring Systems[a]

Compound Position	Cyclohexanes[42]	Piperidines[4]	Hexamethylenimines (present work)
α_e	+5.60		+5.90
β_e	+8.90		+8.18
γ_e	0.00		-1.94
δ_e	-0.03		-0.21
$\alpha_e^{C-2,C-3}$		+5.00	
α_e^{C-4}		+6.00	
β_e		+8.30	
$\gamma_e^{C-2,C-3}$		-0.20	
γ_e^{C-4}		-0.60	
δ_e		-0.90	

---

[a] The superscript on the symbol refers to the substituted ring carbon.

is quite similar in cyclohexanone [44] and hexamethylenimine (+23.0 ppm and +21.33 ppm respectively). In addition, the β_e- and γ_e-effects derived from 4-t-butylcyclohexanone were used to aid the assignments in 4-t-butylhexamethylenimine. The assignments thus obtained for the free amine are reasonable when compared with the chemical shifts of other derivatives. Thus C-6 is predicted to be at 32.31 ppm (observed 30.87 ppm). Calculations of the shifts for the carbon atoms C-3 and 5 are 32.81 and 28.50 ppm, respectively (observed 32.32 ppm and 28.06 ppm). The average values of the C-methylation parameters obtained from 2-methylhexamethylenimine and 4-methylhexamethylenimine are +5.90, +8.18, -1.94 and -0.21 ppm for α, β, γ and δ respectively. Thus, as shown in Table 16, the C-methylation effects in hexamethylenimines exhibits a trend that bears more resemblance to C-methylation in piperidines than in cyclohexanes (Table 17). The γ_e-effect is more shielding in the 7-membered heterocycles. The parameters suggest that there are no conformational changes involved on C-methylation and the alkyl substituents are equatorial in orientation.

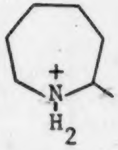
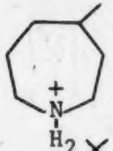
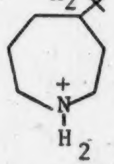
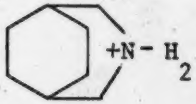
The assignment of the bicyclic octamethylenimine is straight forward. The equivalence of C-6, 7, 8 and 9 is introduced by the rapid inversion of the nitrogen atom and interconversion between the conformers. The molecule has C-methylation parameters different from other hexamethylenimines. C-2 and C-4 are shifted downfield by 6.22 ppm due to the β-subsitution at C-1 and C-5 when compared with hexamethylenimine, whereas C-6, 7, 8 and 9 are shielded by 1.84 ppm due to the same β-substition. An α-effect of +1.30 ppm is observed at positions 1 and 5. The different conformations and ring strain between hexamethylenimine and bicyclic octamethylenimine contribute heavily to the experimental results.

b. N-protonation Effects

The carbon-13 chemical shifts of the hydrochloride salts of hexamethylenimines and the protonation parameters are given in Table 18. The changes in the chemical shifts of these hexamethylenimines upon protonation have been interpreted on the basis of the chemical shifts of the corresponding parent amines and the protonation parameters determined for hexamethylenimine hydrochlorides. These parameters are -3.75 ppm, -4.69 ppm and -2.20 ppm for β, γ and δ, respectively (see Table 9). The deviations from additivity are small. The close agreement is taken as confirmation of correct assignments in the salts. In 4-methylhexamethylenimine hydrochloride, the shifts are calculated to be 43.94, 35.87, 31.57, 33.46, 24.76 and 45.54 ppm for C-2, 3, 4, 5, 6 and 7, respectively. These values

TABLE 18

Carbon-13 Chemical Shifts of the Hydrochloride Salts of Hexamethylenimines and Their Protonation Effects[a]

	Carbon position										
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	Methyl	C-4(q)
		54.97 (-0.05)	33.45 (-5.39)	24.76 (-0.86)	26.76 (-0.54)	24.76 (-6.64)	44.88 (-2.81)			20.34 (-3.77)	
		44.02 (-3.66)	33.72 (-6.84)	32.91 (-0.86)	35.44 (-0.22)	23.53 (5.92)	45.75 (-3.50)			22.82 (-1.19)	
		45.33 (-3.50)	27.66 (-4.66)	48.92 (+0.29)	26.26 (0.29)	24.22 (-6.65)	45.67 (-3.93)			27.37 (-0.10)	33.59 (+0.05)
	28.10 (-4.81)	52.47 (-3.42)	- -	52.47 (-3.42)	28.10 (-4.81)	23.98 (-1.48)	23.98 (-1.48)	23.98 (-1.48)	23.98 (-1.48)		

a. Value of the effect shown in parenthesis for the corresponding carbon.

can be compared with the observed values 44.02, 33.72, 32.91, 35.44, 23.53 and 45.75 ppm. The agreements are thus fairly close. Similarly, the shift values for C-2, 3, 4, 5, 6 and 7 in 2-methylhexamethylenimine hydrochloride, with the predicted values in parentheses, are: 54.97 (51.51), 33.45 (35.15), 24.76 (23.42), 26.76 (25.10), 24.76 (26.71) and 44.88 (44.18). In 4-t-butylhexamethylenimine hydrochloride, the corresponding values are: C-2 45.33 (45.08), C-3 27.66 (27.63), C-4 48.92 (46.43), C-5 26.26 (25.86), C-6 24.22 (26.18) and C-7 45.67 (45.85) ppm. The agreement is even better in the bicyclic octamethylenimine: 52.47 (52.14), 28.10 (28.22) and 23.98 (23.26) for C-2, 4, C-1, 5 and C-6, 7, 8, 9, respectively. The analysis of all the derivatives of the three hexamethylenimines and bicyclic octamethylenimine can be achieved similarly by applying the substituent parameters derived from hexamethylenimine.

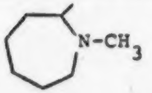
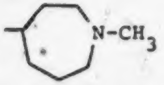
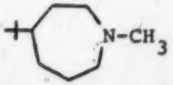
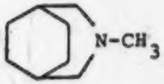
The protonation parameters of the substituted hexamethylenimines and bicyclic octamethylenimine show two interesting differences when compared with the same parameters observed in piperidines and hexamethylenimine. These are: (1) the γ-effects are more shielding in this series, especially in 4-t-butylhexamethylenimine, (2) the δ-parameters are diminished but the effects are still shielding. However, the opposite is true in the case of 4-t-butylhexamethylenimine. Further, C-2 of 2-methylhexamethylenimine is less shielded by 2.76 ppm relative to the other β-carbon, C-7, upon protonation. These observations correlate well with the polarization arguments delineated earlier. Since it is generally agreed that the C-H bond is more easily polarized than the C-C bond, then the carbon with fewer directly bonded hydrogen atoms will receive less negative charge from the hydrogen atoms. Thus, the tertiary carbons are less shielded or practically deshielded relative to secondary carbons even though both types of carbon atoms are equidistant from the site of protonation. This trend has already been found in piperidines.[74] Remote intramolecular electric field effects which were used to explain the anomalous δ-protonation effect need not be invoked in this series. It seems possible the δ-effect is diminished by the alkyl substituents or is changed as the consequence of the nature of the $\overset{\ominus}{C}$-$\overset{\oplus}{H}$ polarization in secondary and tertiary carbon atoms. Theoretical studies are necessary to resolve this problem. No attempt was made to calculate the average protonation parameters for these 7-membered heterocycles as the sites of C-substitution vary and the C-substituents differ.

c. N-methylation Effects

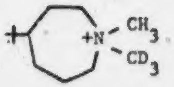
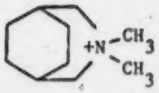
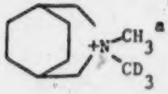
Table 19 provides a list of the carbon-13 chemical shifts of the N-methyl substituted hexamethylenimines and bicyclic octamethylenimine along with the N-methylation

TABLE 19

Carbon-13 Chemical Shifts of Some Methylated Hexamethylenimines and Their N-methylation Effects[a]

	Carbon position										
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-Methyl	N-Methyl	C-4'(q)
	- -	59.34 (+4.32)	35.66 (-3.18)	25.46 (-0.16)	28.16 (+0.86)	28.65 (-2.75)	54.34 (+6.65)			19.69 (-4.42)	41.48	
	- -	56.54 (+8.85)	36.74 (-3.82)	33.34 (-0.43)	35.88 (-0.08)	26.60 (-2.85)	58.85 (+9.53)			23.88 (+0.13)	47.42	
	- -	58.15 (+9.32)	29.08 (-3.24)	48.17 (-0.46)	[27.89] (-0.17)	[27.78] (-3.09)	58.69 (+9.09)			27.35 (-0.12)	47.47	33.55 (+0.01)
	30.59 (-2.32)	65.71 (+9.82)	- -	65.71 (+9.82)	30.59 (-2.32)	25.95 (+0.49)	25.95 (+0.49)	25.95 (+0.49)	25.95 (+0.49)		46.66	

a. Value of the effect shown in parenthesis for the corresponding carbon. [] indicates the assignments are interchangeable within the compound.

		65.49 (+7.34)	23.59 (-5.49)	48.88 (+0.71)	27.94 (+0.05)	21.69 (-6.09)	66.25 (+7.56)			54.27 (+6.80)	54.27 (+6.80)	27.51 (+0.16)	33.50 (-0.05)
	30.19 (-0.40)	73.92 (+8.21)	- -	73.92 (+8.21)	30.19 (-0.41)	24.95 (-1.00)	24.95 (-1.00)	24.95 (-1.00)	24.95 (-1.00)	59.58 (+12.92)	59.58 (+12.92)		
 [a]	31.29 (-0.70)	74.34 (+8.63)	- -	74.34 (+8.63)	31.29 (-0.70)	25.78 (-0.17)	25.78 (0.17)	25.78 (-0.17)	25.78 (-0.17)	59.88 (+13.22)	59.88 (+13.22)		

a. The 2-methyl compounds were ran in deuterium oxide, the rest of the series in deuteriochloroform.

effects observed in these compounds. It is apparent that the N-methyl substituent effects are transferable between cyclohexanes, piperidines and hexamethylenimines. Since the alkyl substituents lift the equivalence of C-2, 7, C-3, 6 and C-4, 5, there are two sets of substituent effects for each compound. Both 1,4-dimethylhexamethylenimine and 1,2-dimethylhexamethylenimine show N-methylation effects similar to those of hexamethylenimine, their β- and γ-carbon which are more remote from the site of the ring carbon-substitution are relatively deshielded. That is, the β-effect observed at C-7 (+9.53 ppm) versus that at C-1 (+8.85 ppm), and the γ-effect at C-6 (-2.85 ppm) compared to that at C-3 (-3.82 ppm) in 1,4-dimethylhexamethylenamine. This indicates the C-methyl substituent affects the electron density distribution in the ring in the N-methylated compounds. The largely attenuated β N-methyl-effect shown by C-2 in 1,2-dimethylhexamethylenimine can be rationalized by the steric interaction between the vicinal 1 and 2-methyl groups.[42] This shields the position C-2 and consequently compensates for the lowering through the substituent effect. The average value of the γ-effects observed in 1,2-dimethyl-, 1,4-dimethyl- and 4-t-butyl- compounds is (-3.20 ppm), comparable to that observed in 1-methylhexamethylenimine. Accordingly, it is quite reasonable to conclude that these four cyclic amines have the same conformation at ambient temperatures with the electron-pair of nitrogen in an axial position. At least this is the preferred conformation. Table 20 shows the average values of methylation effects in hexamethylenimines. This set of values gives a close agreement with those of methylcyclohexanes with the exception of the γ-effect.

Attempts to lock out the conformation of 1-methyl-4-t-butylhexamethylenimine have been carried out but were unsuccessful. The slight changes in the chemical shifts at -105°C may be due to the change of the solvent effect which can be temperature dependent.

The chemical shift value (25.95 ppm) of the δ-carbons in the methylated bicyclic octamethylenimine suggests the presence of rapid inversion of the nitrogen atom with the methyl substituent in the equatorial position. The δ-effect of +0.49 ppm is probably due to the net effect of the δ-shielding provided by N-methylation and deshielding caused by the nitrogen lone-pair in the relatively rigid molecule. If one draws an analogy between this molecule and monocyclic hexamethylenimine, it is expected that the γ-carbon pair will be shielded by the electron-pair of the nitrogen. Experimentally, these carbons, C-1 and 5 are shielded by 2.32 ppm.

d. Methiodation Effects

Table 21 shows the carbon-13 chemical shifts of the

TABLE 20

Average Values of N-methylation Effects in Hexamethylenimines[a]

Position	Average effects
β	+8.75[b]
γ	-3.24
δ	-0.37

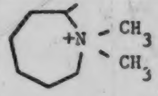
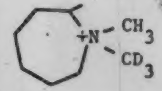
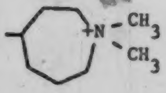
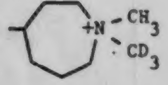
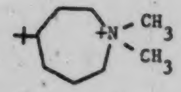
---

a. The calculation does not include the bicyclic hexamethylenimine.

b. The calculation does not include C-2 of 1,2-dimethylhexamethylenimine.

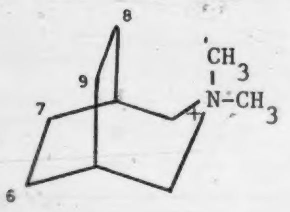
TABLE 21

Carbon-13 Chemical Shifts of Some Hexamethylenimine Methiodides[a] and Their Methiodation Effects

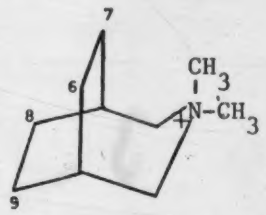
	Carbon position												
Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1'	C-1-1'	C-Methyl	C-4'(q)
		70.78 (+11.44)	29.35 (-6.31)	26.22 (+0.76)	26.71 (-1.45)	21.37 (-7.28)	68.03 (+13.69)			52.66 (+11.18)	47.37 (+5.89)	17.43 (-2.26)	
		70.64 (+11.30)	29.05 (-6.61)	26.04 (+0.58)	26.52 (-1.64)	21.08 (-7.57)	67.78 (+13.44)			52.01 (+10.53)	47.64 (+6.16)	16.96 (-2.73)	
		63.73 (+7.19)	29.98 (-7.76)	33.83 (+0.49)	36.07 (+0.19)	20.53 (-6.07)	65.62 (+6.84)			54.02 (+6.6)	54.02 (+6.60)	22.57 (-1.31)	
		64.99 (+8.45)	29.66 (-7.08)	34.32 (+0.98)	36.31 (+0.43)	21.36 (-5.24)	66.79 (+8.01)			55.62 (+8.20)	55.62 (+8.20)	22.67 (-1.21)	
		65.81 (+7.66)	23.30 (-5.78)	49.04 (+0.87)	28.05 (+0.16)	21.74 (-6.04)	66.52 (+7.83)			54.54 (+7.07)	54.54 (+7.07)	27.51 (+0.16)	33.55 (0.00)

methiodides of the substituted hexamethylenimines and bicyclic octamethylenimine and the corresponding methiodation effects. These methiodides exhibit the same trend as the hexamethylenimines. That is, positions C-2 and 6 are deshielded while other carbons, in general, are shielded. However, the magnitude of the effects are scattered, +7.00 to +14.00 ppm for β-,-0.4 to -7.8 for γ- and -1.6 to +1 ppm for δ-methiodation effect. The shielding effects shown by the γ-carbons indicate there is steric interaction between the N-methyl groups, C-3 and C-6. The ring is locked conformationally in 1,1,2-trimethylhexamethylenimine since two N-methyl signals are observed. These signals are separated by 5.29 ppm in the $CH_3-\overset{\oplus}{N}-CH_3$ compound and 4.37 ppm in the $CH_3-\overset{\oplus}{N}-CD_3$ molecule. Judging the intensity of the resonance peaks, the signal at lower field is due to CD_3 and suggesting that it is axially oriented. The steric interaction between the axial N-methyl group and the protons at C-3, 6 is smaller than the 1,3 syn-axial nonbonded interaction between the equatorial N-methyl substituent and C-methyl group at C-2. Therefore, it is probable that the preferred course of quaternization of the nitrogen is axial. This corresponds with the view of axial orientation of the electron-pair in 1-methylhexamethylenimine. It is tempting to extend these arguments to the course of methiodation in all hexamethylenimine methiodides.

In the bicyclic species, the two N-methyl groups are equivalent and their carbon chemical shifts are relatively deshielded when compared with those in hexamethylenimine methiodides. We, thus, speculate that this molecule is free flipping between the conformations (12) and (13) and the deshielding δ-effect [77] is also



12



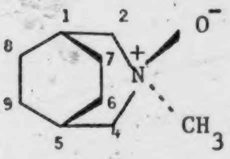
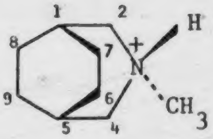
13

operative in this compound.

The N-oxide and hydrochloride salt of the methylated bicyclic octamethylenimine were prepared for further conformational studies. Their chemical shifts and corresponding effects are given in Table 22. There are two pairs of non-equivalent δ-carbons in these derivations. One pair is more shielded than the other by 5.07 ppm in the N-oxide and 4.47 ppm in the hydrochloride salt. The experimental data also indicate the presence of free flipping in these derivatives.

TABLE 22

Carbon-13 Chemical Shifts of the Derivatives of 3-Azabicyclo[3.2.2]nonane and Their Corresponding Substituent Effects

Compound	Carbon position C-1,5	 C-2,4	 C-6,7	 C-8,9	 C-1'
	29.62 (-0.97)	76.12 (+10.41)	27.94 (+1.99)	22.87 (-3.08)	64.57 (+17.81)
	28.49 (-2.10)	63.44 (-2.27)	26.26 (+0.31)	21.79 (-4.16)	45.67 (-0.99)

E. Conclusions

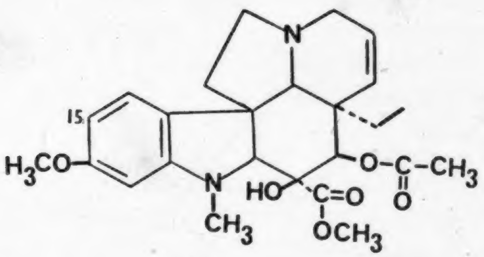
The following conclusions can be drawn. (a) When a $-CH_2-$ is replaced by an $-NH-$ group, heterocycles of sizes ranging from 3- to 9-membered ring type give additive α-parameters of +20.85 ppm, the inductive polarization effect of the electronegative nitrogen atom is the main contributor. (b) Our experimental findings support the view that the electron lone-pair is equatorial in NH compounds and axial in N-methylated molecules. (c) the C-H bond is polarized to the $\overset{\ominus}{C}-\overset{\oplus}{H}$ form when the cyclic amine is protonated, the electron of the hydrogen atom is polarized towards the positively charge nitrogen through the σ-carbon skeleton. The attenuating and alternating feature of the protonation effects observed corresponds well with the attenuation and alternation in the σ-inductive effect predicted by Pople et al.[75] The general trend of protonation shieldings found in hexamethyleniimines follows the order of secondary carbon > tertiary carbon > quaternary carbon. Moreover, 7-, 8- and 9-membered heterocycles, in general, exhibit γ-protonation effects which are conformationally dependent and their values agree with theoretical calculations. (d) The order of methylation and methiodation parameters obtained in hexamethylenimine are similar to those in piperidines, though the magnitudes are different. However, the differences can be rationalized by the change of conformation upon reaction. This is also true for 8- and 9-membered rings. (e) N-oxidation shows additivity trends similar to that of methiodation, but the effects tend to be more deshielding. (f) In sterically congested environments the lone-pair of the nitrogen atom, in general, shields the ring carbons in the heterocycles studied.

It is obvious that this cmr study furnishes useful conformational information on nitrogen heterocycles and their derivatives, especially on 7-, 8- and 9-membered ring systems. Various substituent parameters which are mainly governed by the ring conformations may be applied to aid the assignments of the complex alkaloids investigated in later chapters.

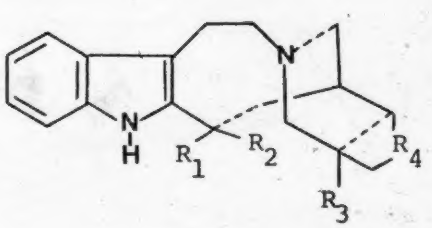
III Carbon-13 NMR Analysis of Some Vinca Monomeric and Dimeric Alkaloids

A. Introduction

Wenkert and co-workers [78] have reported the carbon-13 analysis of the Aspidosperma alkaloid vindoline (14) which was subsequently used as a model system in the partial analysis of two naturally occurring vinca alkaloids vincaleukoblastine (VLB) (15) and leurosine (16). Most of the saturated carbons in the carbomethoxyvelbanamine portions of the two dimers were not assigned. In



14



	R_1	R_2	R_3	R_4
15	CO_2CH_3	15-vindolinyl	OH	H
16	CO_2CH_3	15-vindolinyl	O	

spite of the difficulties involved in the additivity considerations for the analysis of the non-rigid 9-membered heterocyclic constituent in carbomethoxyvelbanamine, and the complexity of the sfor decoupled spectra of the dimer species, we have chosen six cleavamine molecules, catharanthine, and two indole-vindoline dimers for the present study to show that a better if not complete cmr analysis may be feasible for alkaloids of similar type. By using selective proton decoupling technique, additivity relationships, background systems such as piperidines, hexamethylenimines, octamethylenimines, indole, vindole and 2-carboethoxy-2-azabicyclo-[2.2.2]oct-5-ene, and intercomparisons of chemical shifts between these structurally related compounds, unambiguous assignments of nearly all the resonances have been made. The outcome of this work shows the potential of cmr spectroscopy as a probe to study the conformation of both monomeric and dimeric alkaloids. In the latter case, this is critically important since it has been shown that conformation is a critical determinant of their medicinal properties.

B. Experimental

Carbon-13 spectra were determined in the Fourier mode using either a Bruker HFX-90 spectrometer or a Varian Associates HA-100D-15 spectrometer as described in Chapter II. Pmr spectra were obtained on a Varian Associates HA-100. The δ-scale is used to express the chemical shift values of both carbon-13 nmr and pmr spectra.

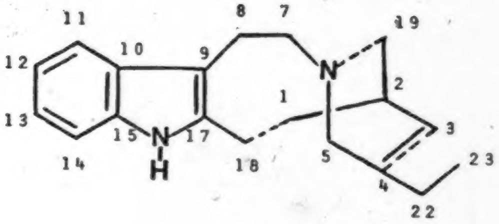
The cleavamine and catharanthine alkaloids were kindly supplied by Dr. J. P. Kutney of the University of British Columbia and were used directly without further purification.

All the samples were run as saturated solutions in deuteriochloroform with internal TMS as an internal reference.

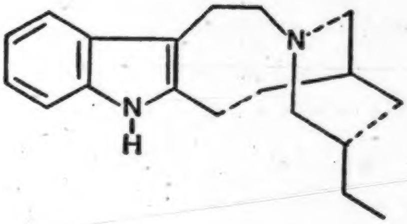
2-Carboethoxy-2-azabicyclo[2.2.2]oct-5-ene was synthesized using the procedure of Cava and co-workers[79], b.p. 55 - 63° (3 mm) (lit.[79], 58 - 64° (3mm)).

C. Results and Discussion

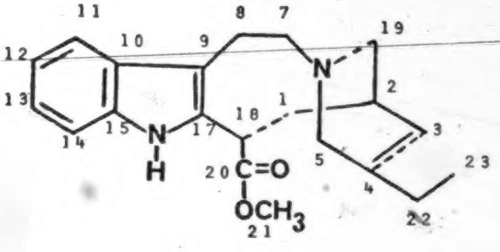
Structures, conformations and numbering systems for the alkaloids cleavamine (17), dihydrocleavamine (18), 18β-carbomethoxycleavamine (19), 18β-carbomethoxydihydrocleavamine (20), 3-hydroxy-18β-carbomethoxydihydrocleavamine (21), catharanthine (22) are shown in Figure 9. The carbon-13 chemical shifts of these alkaloids are



Cleavamine 17

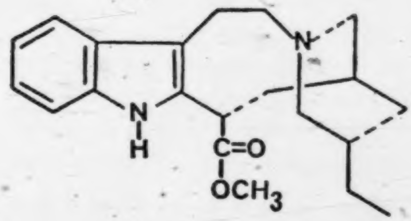


Dihydrocleavamine 18

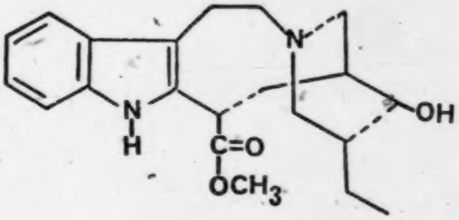


18β-carbomethoxycleavamine 19

FIGURE 9. Structures of the Vinca Alkaloids Studied.

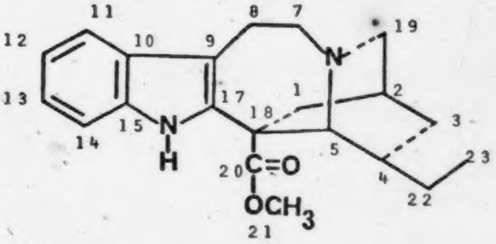


18β-carbomethoxydihydrocleavamine 20



3-hydroxy-18β-carbomethoxydihydrocleavamine

21



Catharanthine 22

summarized in Table 23. For clarity, the data are also shown in a correlation diagram (Figures 10a,b). Table 24 gives the pmr δ values of the specific protons irradiated in the proton selective decoupling experiments.

The experimental procedure for collecting carbon-13 chemical shift data and the techniques used for spectral assignments were described in Chapter I. The noise and sfor decoupled spectra of 18β-carbomethoxydihydrocleavamine (**20**) are shown in Figure 11 to illustrate the determination of substitution pattern for the individual carbon resonances. Selective proton decoupling was also found to be valuable in the study. As an example we choose catharanthine (**22**). The 100 MHz pmr spectra of (**22**) is shown in Figure 12. Proton decoupling at a frequency corresponding to the pmr δ value of 1.0 ppm which has been assigned to H-23 causes the collapse of the cmr resonance at 10.8 ppm to a singlet with enhanced intensity while the other carbons show residual couplings (compare (a) with (b) in Figure 13). The sfor decoupled spectrum of catharanthine (**22**) ranging from 200 Hz to 1700 Hz ((b) in Figure 13) is used as a reference. This confirms that the carbon-13 resonance at 10.8 ppm is due to C-23. Similarly when the decoupler frequency is set at 3.11 ppm (H-8), the cmr signal at 21.52 ppm, which had previously been assigned to C-8 stays a sharp singlet (compare (c) with (b) in Figure 13). As a result, this

TABLE 23

Carbon-13 Chemical Shifts in Selected Vinca Alkaloids[a]

Carbon Position	Compound[b]							
	17	18	19	20	21	22	39a	40a
C-1	26.11	26.21	26.43	26.54	26.43	38.73†	43.86	46.07
C-2	35.44	35.18	34.85	34.90	43.05	30.91	31.77	(36.09)
C-3	122.62	31.34	112.65	31.18	73.85	123.59	(36.74)	42.83
C-4	140.75	32.91	141.61	32.26	40.89	149.49	28.65	28.59
C-5	(53.62)	51.63	(53.19)	(51.36)	(51.20)	61.88†	54.11	54.00
C-7	(53.95)	52.38†	(53.78)	(52.00)	(51.95)	53.14†	53.25	53.24
C-8	34.15	33.82†	38.41	38.68†	35.93	21.52†	22.28	21.63
C-9	109.94	110.00	110.64	112.05	111.83	110.86	111.40	111.78
C-10	128.82	128.54	128.01	127.91	127.75	129.15	128.34	129.31
C-11	118.79	118.84	119.06	119.06	119.17	119.44	118.67	118.68
C-12	120.68	120.73	121.97	121.65	121.76	121.86	119.65	121.06
C-13	117.82	117.82	118.36	118.30	118.25	118.20	117.82	117.77
C-14	109.94	110.00	117.78	110.70	110.75	110.43	110.59	110.10
C-15	135.51	135.62	(134.70)*	134.06	133.90	135.14	133.68	135.51
C-17	139.40	138.70	(135.89)*	136.16	136.16	136.54	134.81	137.11
C-18	22.55	21.30	38.73	37.71†	38.46	55.62	53.25	(38.79)
C-19	55.13	58.90	55.35	59.07	57.03	49.58	44.99	53.24
C-20	-	-	175.81	176.50	175.22	174.14	175.22	-

(continued........)

TABLE 23 (continued)

C-21	-	-	52.06	52.00†	52.17	52.22	51.22	-
C-22	27.67	28.75	27.73	28.70†	24.76	26.27†	(36.52)	35.77
C-23	12.68	11.65	12.62	11.65†	10.79	10.80†	11.54	11.65

---

a. Values in ppm downfield from TMS and this definition is applied to the all values listed in tables in this Chapter. † Denotes carbon assignment confirmed by proton selective decoupling. Values in parentheses and ( )* indicate they are interchangeable within the molecule due to the small difference in chemical shift values.

b. 39a and 40a represent the dihydrocleavamine portion of dimers (39) and (40) respectively.

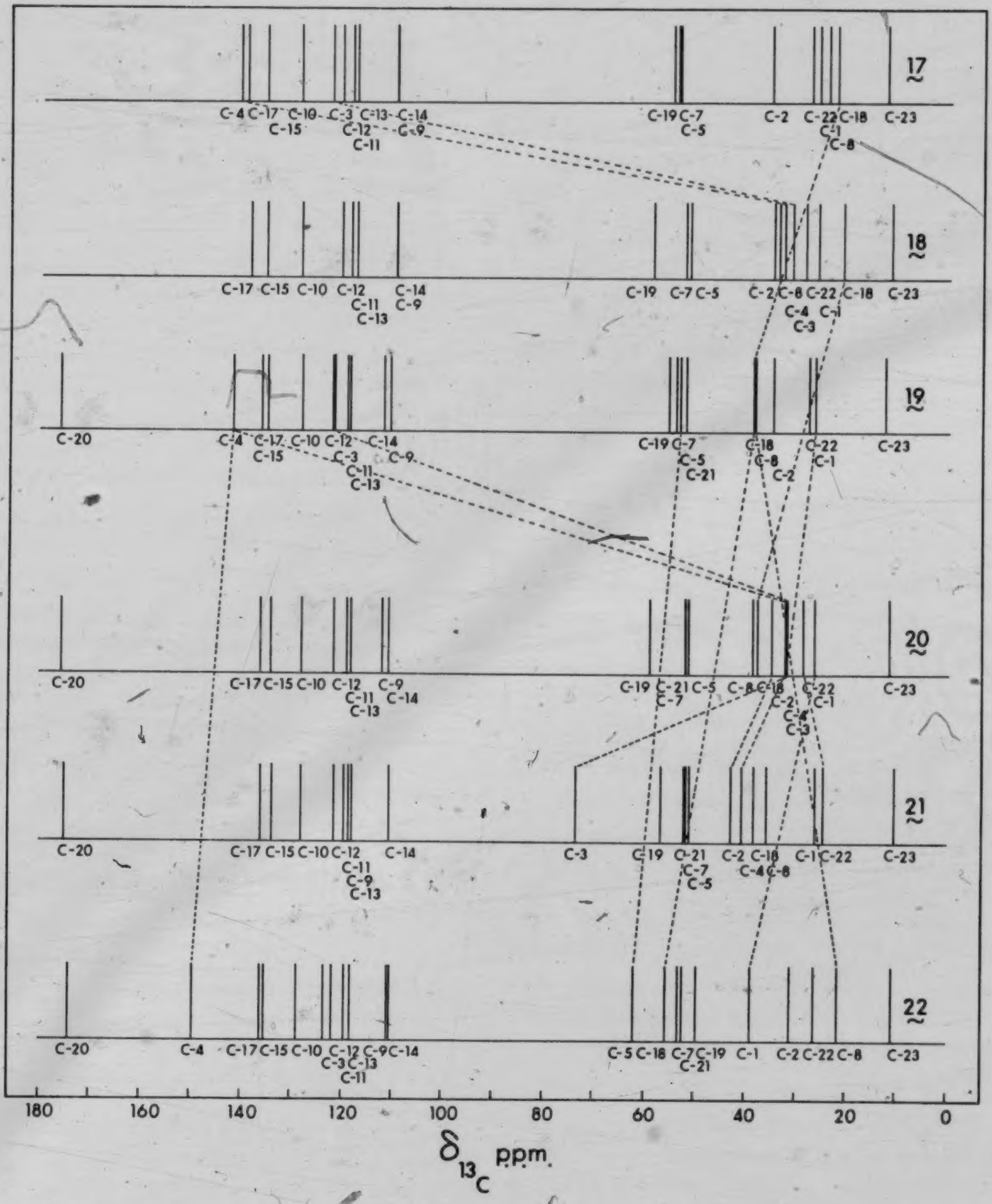


FIGURE 10a. Carbon-13 Chemical Shift Correlations Showing Shifts and Assignments in the Vinca Alkaloids Studied.

FIGURE 10b. Carbon-13 Chemical Shift Correlations Showing Shifts and Assignments in the Dihydrocleavamine portions (**39a** and **40a**) of the Indole-Vindoline Dimers (**39** and (**40**) and Monomeric Dihydrocleavamines (**20** and **18**).

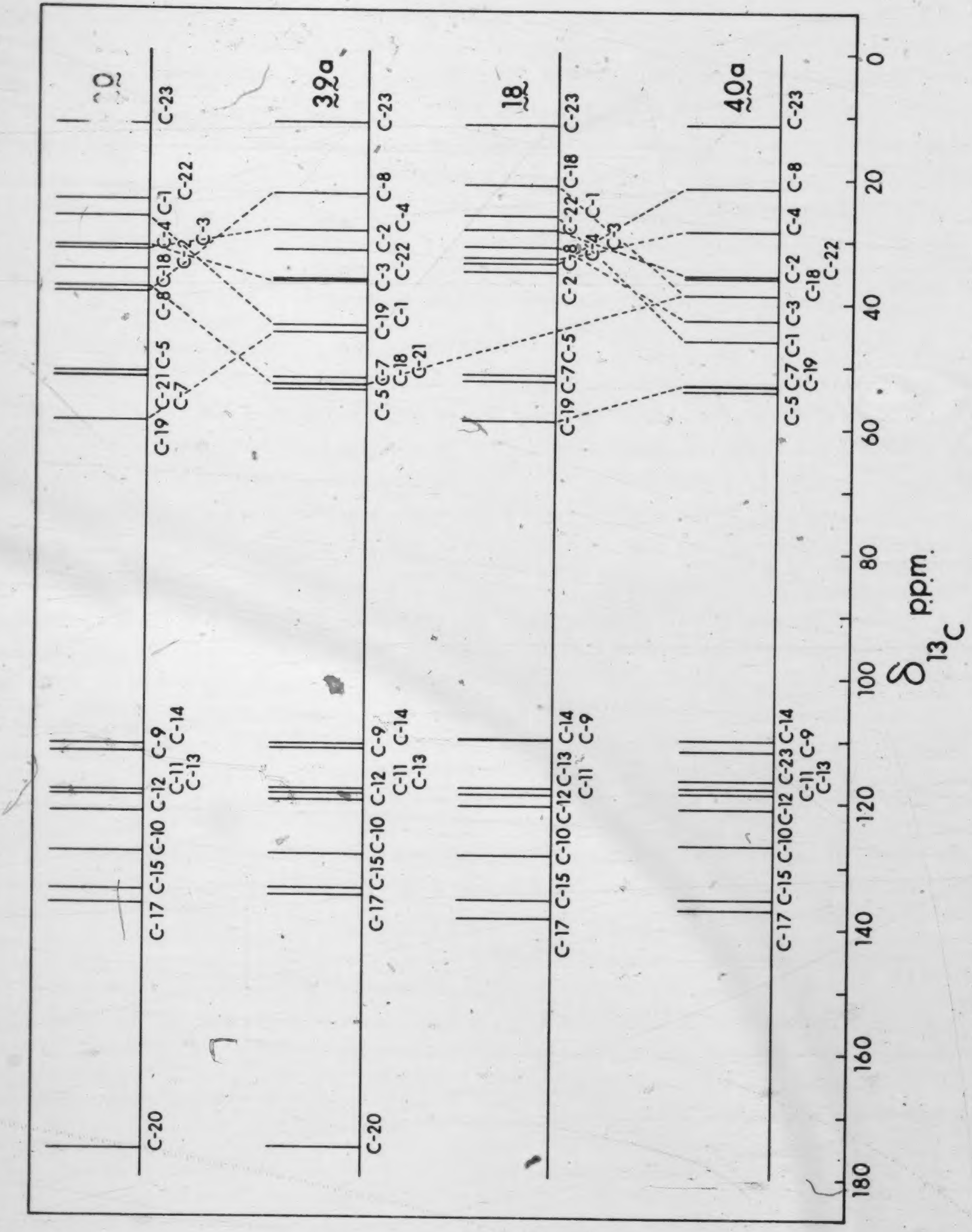

39a
18
40a
C-23
C-22
C-1
C-4
C-2
C-3
C-18
C-8
C-5
C-21
C-7
C-19
C-9
C-14
C-11
C-13
C-12
C-10
C-15
C-17
C-20
0
20
40
60
80
100
120
140
160
180
δ13C p.p.m.

TABLE 24

PMR Chemical Shifts of the Protons Irradiated in Proton Selective Decoupling Experiments of Selected Vinca Alkaloids

Proton	Compound		
Position	**18**	**20**	**22**
H-1			1.65
H-2			2.70
H-5			4.10
H-7	2.58		3.40
H-8	1.80	2.76	3.11
H-18		5.00	
H-19			
H-21		2.65	
H-22	1.24	1.25	2.15
H-23		0.85	1.00

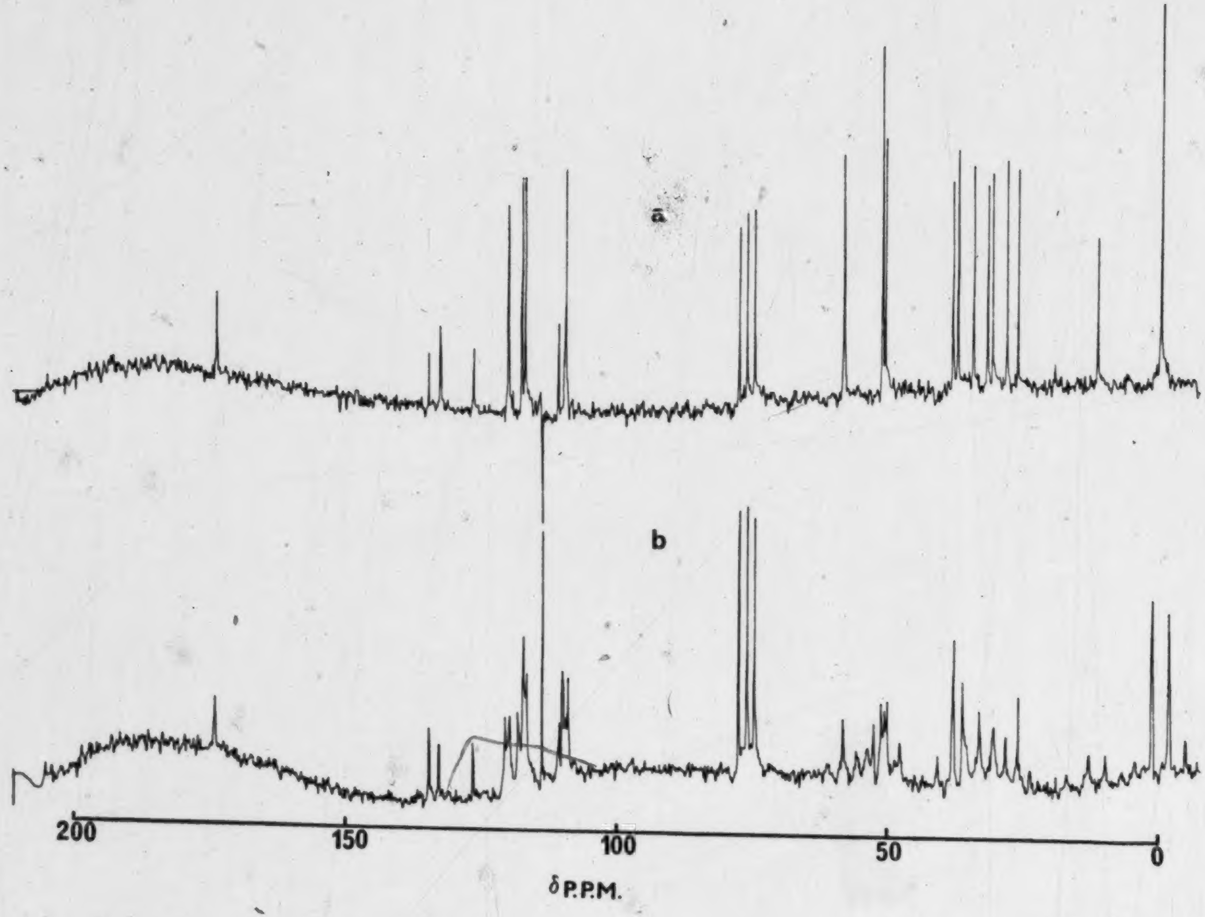


FIGURE 11. Noise (a) and Single Frequency Off-Resonance (b) Decoupled Spectra of 18β-Carbomethoxydihydrocleavamine (20). (The sharp signal at approximately 115 ppm is a noise spike).

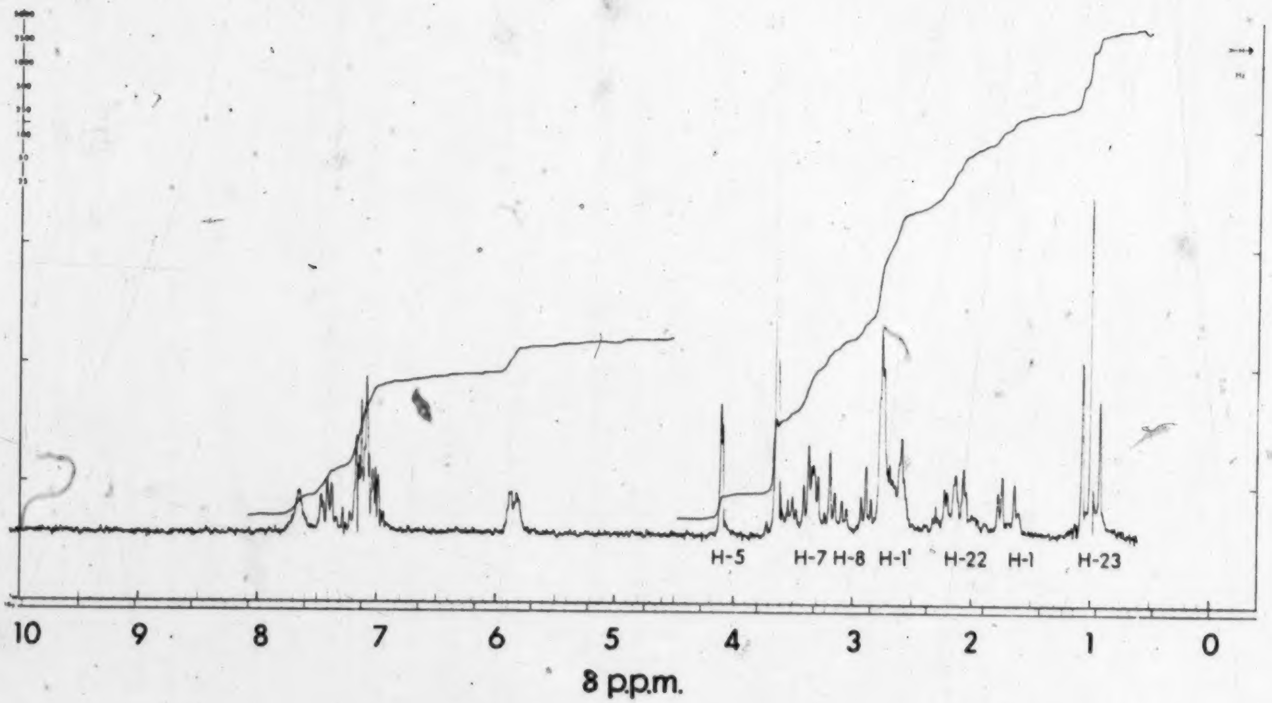


FIGURE 12. 100 MHz PMR Spectrum of Catharanthine (22).

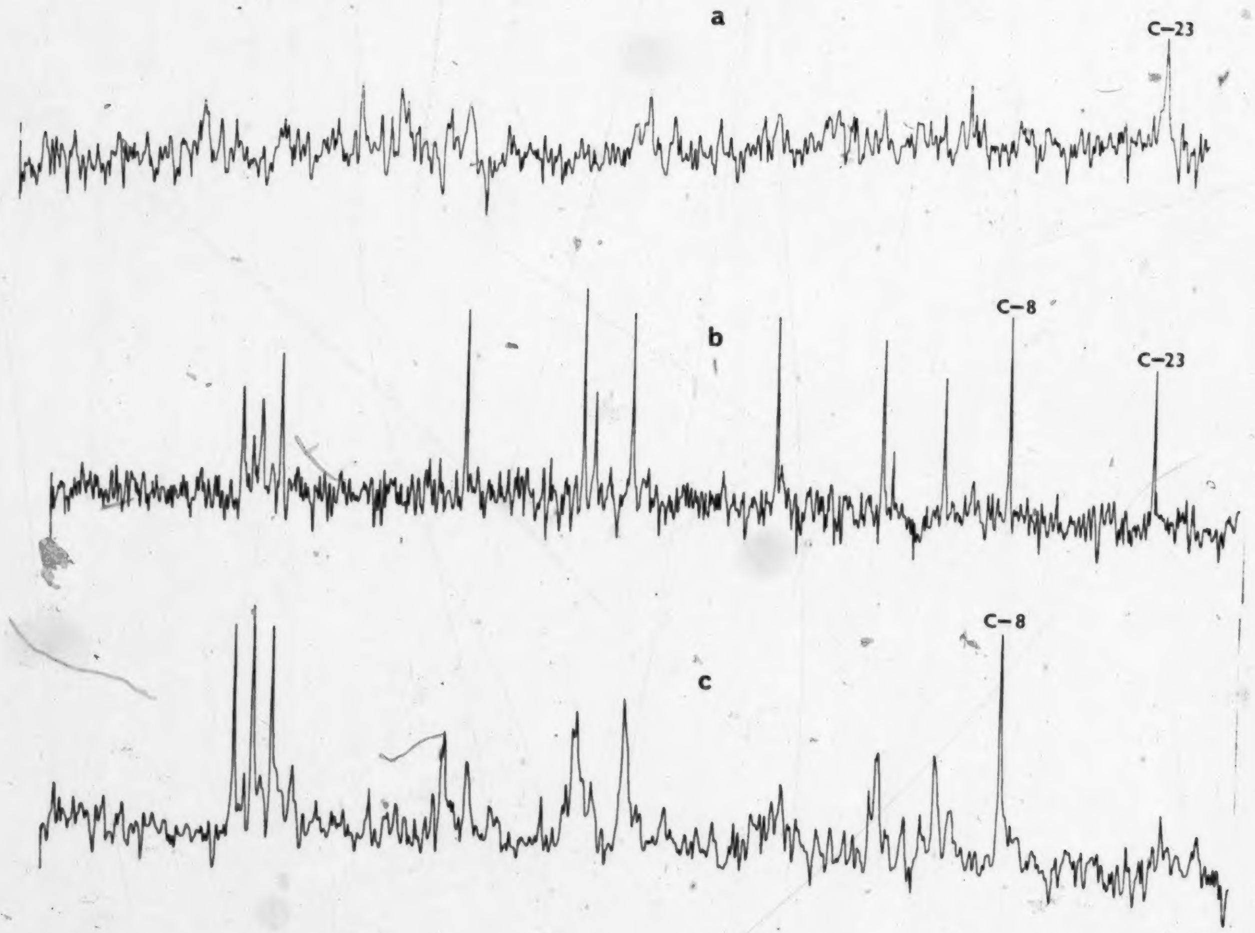


FIGURE 13. Carbon-13 Magnetic Resonance Spectra of Catharanthine (22). (a) Proton H-23 Decoupled Spectrum. (b) Noise Decoupled Spectrum (200 Hz to 1700 Hz). (c) Proton H-8 Decoupled Spectrum.

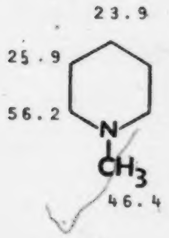
resonance can be assigned to C-8 unambiguously. In addition, several model systems have been used to determine factors such as substituent effects, steric interactions, strain and conformation in these molecules.

The noise decoupled spectrum of cleavamine (17) exhibits individual resonances for all of its twenty-one carbon atoms. The peaks appear in two distant groups, those corresponding to unsaturated carbons at low field and those corresponding to saturated carbons at high field. There are ten resonances in the low field region of the spectrum. The aromatic carbons C-9, 10, 11, 12, 13 and 14 were assigned by analogy to Roberts' analysis of selected indoles.[80]

Comparison of the spectrum of cleavamine (17) with that of 3,4-dihydrocleavamine (18) shows that the resonances at 122.62 ppm and 140.75 ppm shift upfield on hydrogenation. At the same time, new resonances occur at 32.91 ppm (CH) and 31.34 ppm (CH_2) in the dihydro derivative. The region between 30 - 35 ppm was previously unoccupied by any resonance in (17). Therefore, the resonances at 122.62 ppm and 140.75 ppm are assigned to the olefinic methine carbon C-3, and the quaternary carbon C-4, respectively, in cleavamine (17) and 31.34 ppm and 32.91 ppm to the corresponding carbon atoms in dihydrocleavamine (18). A similar difference is observed in the spectra of 18β-carbomethoxycleavamine (19) and 18β-carbomethoxydihydrocleavamine (20), enabling assignments of C-3 and 4 for this pair of molecules.

The remaining amino-quaternary sites at C-15 and C-17 in cleavamine (17) are distinguished from each other by the shift of the former being invariable in the spectra of cleavamine (17) and 18β-carbomethoxycleavamine (19), while the latter reflects a β-carbomethoxy substituent effect (-3.51 ppm) in (19). The quaternary carbons C-15 and C-17 in dihydrocleavamine (18) and 18β-carbomethoxydihydrocleavamine (20) are similarly assigned. The indole portion of the 3-hydroxy-18β-carbomethoxydihydrocleavamine (21) can be assigned by comparison with the spectra of the other four cleavamines. This completes the analysis of the aromatic and unsaturated portion of these five structurally related alkaloids. Somewhat unexpectedly the carbomethoxy group produces a β-shielding effect (-3.51 ppm in (19) and -2.54 ppm in (20)) on the aromatic carbon C-17 in these alkaloids, no explanation can be offered at this stage.

In cleavamine (17) and dihydrocleavamine (18) the carbon atoms C-2 and C-23 are readily recognized since these carbons are the most shielded methine and methyl carbons, respectively. The carbomethoxy methyl carbon in 18β-carbomethoxycleavamine (19) and 18β-carbomethoxydihydrocleavamine (20) can be differentiated from C-23 as the former is deshielded due to its direct bonding to the electronegative oxygen atom. By analogy with the chemical shifts in the model systems (see methylated piperidine and octamethylenimine described in Chapter II), the three resonances in the region of 50 - 60 ppm must be attributed to the aminomethylene carbons C-5, 7 and 19 in these alkaloids. The assignment of C-7 is made by the constancy of its chemical shifts in the five cleavamines. Proton selective decoupling experiments confirmed the predicted assignment in the case of dihydrocleavamine (18). This compound (18) was selected for the selective decoupling experiment since it was the only one which gives a well resolved pmr spectrum in the aliphatic region. Wenkert and co-workers [78] have correlated the effect of incorporation of a double bond into a piperidine ring. Their observations suggest a general shielding effect on homoallyl carbon atoms, for example, the endocyclic homoallyl effect is exhibited by C-6 in (25) and (26), C-2 in (27), C-5 and 6 in (29) and C-6 in (30). Applying this principle to the alkaloids under present considerations, C-19 in cleavamine (17) and 18β-carbomethoxycleavamine (19) would be expected to be shielded when compared with the same carbon in dihydrocleavamine (18) and 18β-carbomethoxydihydrocleavamine (20), respectively. The resonance at 52.38 ppm can be assigned to C-7 of dihydro-



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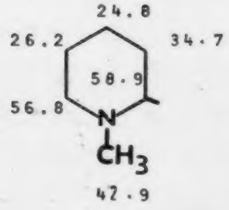

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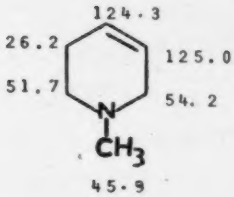

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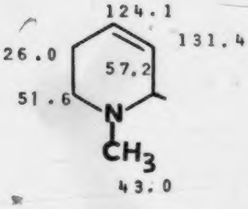

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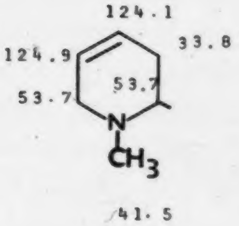

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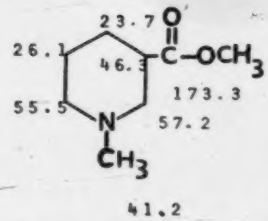

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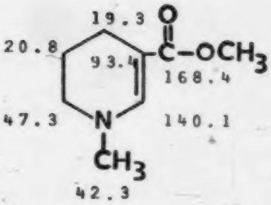

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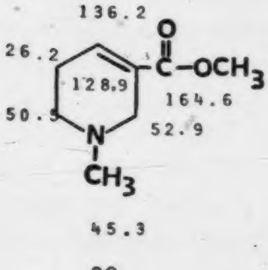

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cleavamine (18) as confirmed by the selective proton decoupling experiment. Thus it is logical to assume one of the two peaks at 53 ppm may be due to C-7 in cleavamine (17) since the shielding of C-7 should remain invariable in these two molecules. Taking these two rationalizations into consideration, the resonance at 58.90 ppm can be assigned to C-19 of dihydrocleavamine (18). The assignment gives a shielding endocyclic homoallyl effect at C-19 in cleavamine (17) when either the resonance at 55.13 ppm or at 53.62 ppm is assigned to the aminomethylene carbon. The last aminomethylene carbon at 51.63 ppm has to be due to C-5 in dihydrocleavamine (18) and subsequently C-5 of cleavamine (17) will be deshielded because of the γ-effect of the double bond at $C_3 - C_4$. This deshielding effect at C-5 cannot be regarded as a complement to the endocyclic homoallyl effect in the assignments of C-5 and C-19 because variable changes in both magnitude and direction are shown by allylic carbons when a double bond is introduced into a piperidine ring. This is particularly apparent when the chemical shift values of 1-methylpiperidine (23), 1,2-dimethylpiperidine (24) and 1-methyl-3-carbomethoxypiperidine (28) are compared with those of 1-methyl-3-piperideine (25), 1,2-dimethyl-3-piperideine (26) and 1-methyl-3-carbomethoxypiperideine (30). The endocyclic homoallyl effect is thus taken as the main determinant for the distinction of C-5 and C-9 in the dihydrocleavamines (18) and (20). The assignments of C-5 and C-19 in cleavamine (17) and 18β-carbomethoxycleavamine (19) can be resolved by the assigned chemical shifts in catharanthine (22). C-5 of catharanthine (22) resonates at 61.88 ppm, this is confirmed by selective proton decoupling and leads to the assignment of the peak at 53.19 ppm to the same carbon in 18β-carbomethoxycleavamine (19). As a consequence C-5 in (19) is deshielded by 8.68 ppm on cyclization; this value seems appropriate as C-5 is now substituted by C-18 in catharanthine (22). This leaves the last aminomethylene resonance at 55.35 ppm to C-19 in 18β-carbomethoxycleavamine (19). By analogy with the assigned chemical shifts of (19), C-5 and C-19 of cleavamine (17) may be idenitified with the resonance at 53.62 ppm and 55.13 ppm, respectively. Following the same argument, C-5, 7 and 19 of 3-hydroxy-18β-carbomethoxydihydrocleavamine (21) may be assigned.

Proton selective decoupling confirms the assignment of the exocyclic methylene C-22 in dihydrocleavamine (18) and 18β-carbomethoxydihydrocleavamine (20). This aids the identification of the same carbon in cleavamine (17) and 18β-carbomethoxycleavamine (19). In both cases, the double bond shields the exocyclic α-carbon atom.

The deshielding property of the carbomethoxy group helps to differentiate C-18 in the cleavamines. The methylene carbon at 22.55 ppm can be assigned to C-18 in cleavamine (**17**) as this resonance shifts downfield 16.18 ppm in 18β-carbomethoxycleavamine (**19**). By analogy, the carbon atom C-18 is assigned in the dihydro derivatives. The carbonyl carbon C-20 can easily be picked out in (**19**) (**20**) and (**21**) on the basis of its characteristic low field shift.

The remaining methylene carbons are C-1 and C-8 in each of the compounds (**17**) to (**21**). The carbomethoxy-substituent effect in octamethylenimine has not been investigated. Therefore, a suitable model compound 1-methyl-3-carbomethoxy-piperidine (**28**) was chosen. The carbomethoxy parameters derived from (**28**) are listed in Table 25. It has been reported [4] that the β-effect of the carbomethoxy group in some indole alkaloids is smaller than that of the methyl substituent. Comparison of the chemical shift values for the unassigned methylenes in cleavamine (**17**) and 18β-carbomethoxycleavamine (**19**) shows that one of the carbon-pairs differ by 4.26 ppm and the other by 0.32 ppm. The carbon in cleavamine (**17**) is the more shielded in both cases. The resonance found at about 26 ppm can be assigned to C-1 in these molecules

TABLE 25

Substitution Effects for Carbomethoxy Group in 1-Methyl-3-Carbomethoxypiperidine

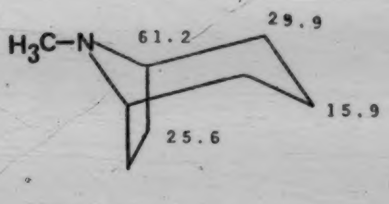
Effect	Values (in ppm)
α	+20.4
β	+ 0.6[a]
γ	+ 0.2
δ	- 0.7

---

[a] Average of +1.0 and +0.2

on the basis of the expected carbomethoxy β-effect. Consequently, the other methylene signal has to arise from C-8. Assuming the structural conformations of these alkaloids are very similar, C-1 and C-8 in the dihydro molecules (**18**), (**20**) and (**21**) can also be characterized by extrapolating the chemical shifts of the corresponding carbons in cleavamine (**17**) and 18β-carbomethoxycleavamine (**19**).

The hydroxymethine carbon C-3 in 3-hydroxy-18β-carbomethoxydihydrocleavamine (**21**) can be easily assigned to the resonance at 73.85 ppm due to the characteristic deshielding γ-effect (~+40 ppm) of the OH substituent.[43] Methine carbons C-2 and 4 can also be recognized by comparison with the chemical shifts of 18β-carbomethoxydihydrocleavamine (**20**) as they are predicted to be deshielded by approximately 10 ppm due to the hydroxy at C-3. A comparison of the chemical shift value of (**31**) and (**32**) gives the effect of hydroxy group on a flattened piperidine ring.



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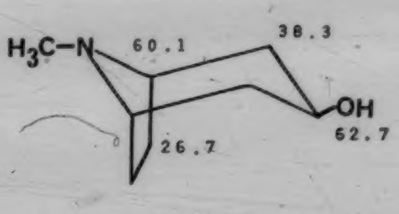

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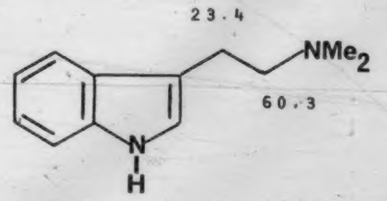
N,N-dimethyltryptamine (33) has been used as a model for the cmr analysis of a number of indole alkaloids, for example, (34) and (35). It is surprising that the carbon atom C-8 in the five cleavamines is deshielded by approximately 10 ppm compared with the chemical shift value of the corresponding carbon in (33). Selective proton decoupling, however, unambiguously confirms this assignment for C-8 in the dihydrocleavamines (18) and (20). This observation indicates that great caution must be exercised in choosing suitable model systems and clearly in these cases a nine membered ring derivative of the type (36) would be preferable though at present synthetically unavailable.



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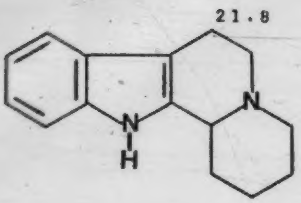

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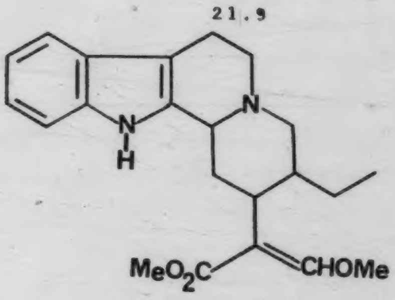

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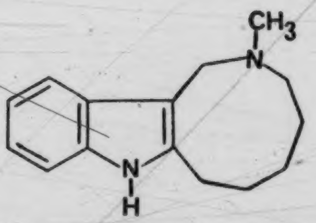

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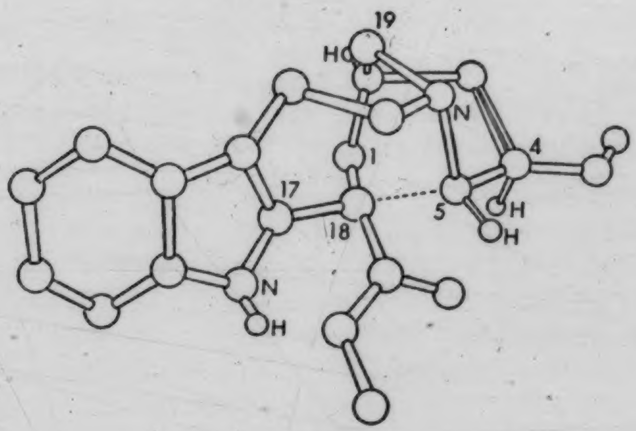
Catharanthine (22), a major alkaloid in Vinca rosea Linn, can be synthesized from 18β-carbomethoxycleavamine (19) by transannular cyclization.[81] As these two molecules are closely related in structure, spectral assignments which have already been obtained for the starting material can be used to aid the assignments of the resonances in the cyclized product. More important the proton spectrum of catharanthine (22) is well resolved and enables confirmation of many of the ^{13}C assignments by selective proton decoupling.

The indole portion of 18β-carbomethoxycleavamine (19) remains intact on cyclization. Thus, the aromatic carbons of catharanthine (22) are expected to resonate at similar portions in these molecules as shown in Table 23. The unique olefinic carbons C-3 and C-4 in (22) are also assigned without ambiguity.

Multiplicities from sfor decoupling and chemical shift argument enable the assignments of the two methyl carbons C-21 and C-23, the carbonyl carbon C-20, the quaternary carbon C-18, and the two methine carbons C-5 and C-2. Both C-18 and C-5 are deshielded in catharanthine (22) since they become more substituted on ring closure. A'priori, the two aminomethylene signals at 49.58 ppm and 53.14 ppm can be assigned to C-19 and C-7. Confirmation of the latter assignment was possible by proton selective decoupling and the former by elimination. Despite the numerous conformations that 18β-carbomethoxycleavamine (19) can attain, there is only one which allows C-18 and C-5 to come into reasonable proximity for bond formation. This is the conformation (37). Reconciliation



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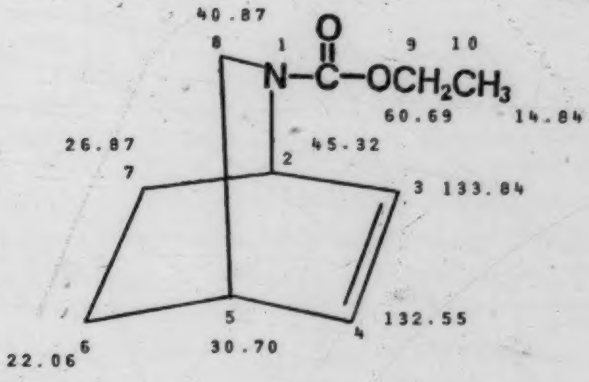
of the above C-13 chemical shifts not only favors (37) as the intermediate in the transannular cyclization but also confirms the structure of (19).

The exocyclic methylene carbon C-22 of catharanthine (22) is predicted to exhibit a chemical shift value similar to that in 18β-carbomethoxycleavamine (19). It is found to be correct experimentally since the assignment of C-22 (26.27 ppm) in (22) is confirmed by proton selective decoupling. The model compound 2-carboethoxy-2-azabicyclo[2.2.2]-oct-5-ene (38) was synthesized to help resolve the assignments of C-1 and C-8 in (22). The ε-effect of carboethoxy and methyl group may be considered as negligible on C-6 in the bicyclic species (38). Thus, the chemical shift value of C-6 in (38) can be extrapolated to that of C-1 in catharanthine (22) as long as an additional β-effect from the 18β-carbomethoxy group and C-17 of the indole double bond are added. It is clear that the chemical shift value of C-1 should be deshielded relative to C-6 in (38) regard-



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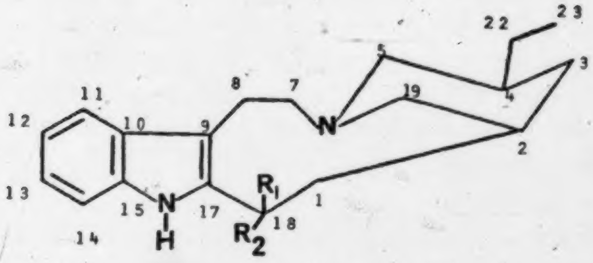
less of the magnitude of the two β-substituent effects. Hence the resonance peak at 38.73 ppm is assigned to C-1 and that at 21.52 ppm to C-8 in (**22**). Another way to rationalize the chemical shift value of these carbons is that C-1 suffers a deshielding β-effect from C-5 on ring closure. It is quite possible that the substituent $\left(\begin{smallmatrix}N_6\\ C_4\end{smallmatrix}\!>C_5-\right)$ deshields C-1 by 12.30 ppm as β-effects of this size have already been encountered in our earlier studies (see Chapter II). Careful examination of the molecular structure of catharanthine (**22**) shows that C-4 is another carbon which experiences a β-effect from C-18 on cyclization. This olefinic methine is also deshielded by 7.88 ppm due to the β-effect exerted by C-18. The high field shift, 21.52 ppm, exhibited by C-8 in catharanthine (**22**) can be accounted for in a number of ways: (a) Possible 1,3 syn-axial steric interaction between C-8 and C-11. This steric congestion is allowed in the conformation of (**22**) and is previously absent in 18β-carbomethoxycleavamine (**19**). (b) Rigidity of the 7-membered constituent in the cyclized molecule as compared to the flexibility of the 9-membered ring in (**19**). (c) Slight transannular repulsion between the proton of C-8 and C-19 which is now acquired by (**22**). The confirmation of the assignments of C-1 and C-8 was obtained by proton selective decoupling experiments. Accordingly, the analysis of this complex alkaloid is complete.

In view of our success in the analysis of cleavamine alkaloids and the cmr studies on vindoline by Wenkert and co-workers [78] (which we have confirmed), we are equipped for the more challenging task of analyzing the dimeric Vinca alkaloids (39) and (40) whose structures are shown in Figure 14. The numbering system for the dihydrocleavamine portion of (39) and (40) follows that of the monomeric alkaloids. The noise off-resonance decoupled spectrum of the two compounds show all carbon resonance peaks and fortunately the substitution pattern of each individual carbon nucleus can be identified in spite of their highly complicated sfor decoupled spectra.

The carbon-13 nmr spectrum of vindoline (14) has been recently analyzed by Wenkert [78] and independently confirmed by proton selective decoupling measurements in the present work. Based on the structural similarities, chemical shift values of vindoline (14) may be applied to the dimeric species (39) and (40). The carbon-13 chemical shifts of vindoline, and the vindoline portion of (39), (40) and VLB (15) [78] are summarized in Table 26. The similarities of the values show that the vindoline constituent in the three dimers are equivalent in structure and indicate that cmr is a most valuable tool in structural studies.

The cleavamine portion of (39) is similar to that in



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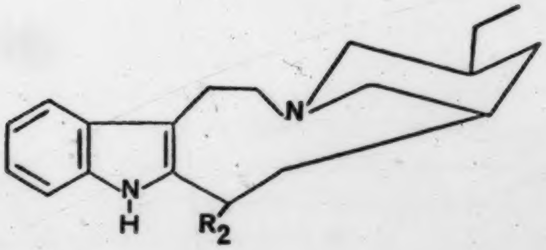

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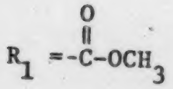


$R_1 = -\overset{\overset{\displaystyle O}{\|}}{C}-OCH_3$

R_2 =

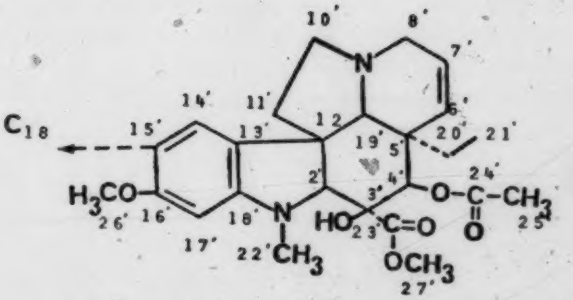


FIGURE 14. Structures of the Vinca Dimers Studied

TABLE 26

Carbon-13 Chemical Shifts of Vindoline and Vindolinyl Portions of Selected Dimers

Carbon Position	Compound			
	14	15[78]	38	40
C-2'	83.56	83.1	83.02	83.29
C-3'	79.73	79.3	79.95	79.89
C-4'	76.49	76.4	76.60	76.44
C-5'	43.10	42.3	42.89	42.83
C-6'	130.66	129.7	130.55	130.55
C-7'	124.08	124.1	124.40	124.40
C-8'	51.19	50.0	50.93	50.87
C-10'	52.11	50.0	50.93	50.87
C-11'	44.13	44.3	43.86	43.75
C-12'	52.92	52.8	53.25	53.24
C-13'	125.21	122.41	126.05	125.70
C-14'	122.73	123.3	121.60	121.38
C-15'	104.71	120.8	124.40	123.91
C-16'	161.35	157.6	156.3	156.82
C-17'	95.97	93.8	94.46	93.70
C-18'	153.86	152.2	152.02	151.75
C-20'	30.91	30.5	30.75	30.64
C-21'	7.71	8.1	7.71	7.71
C-22'	38.25	38.0	38.30	38.14
C-23'	170.74	170.2	170.78	170.79
C-24'	171.98	171.2	171.60	171.66
C-25'	21.04	20.7	21.09	21.04
C-26'	55.40	55.3	56.05	55.89
C-27'	52.11	51.8	52.11	52.06

18β-carbomethoxydihydrocleavamine (20) and therefore the latter compound was chosen as a model. Due to the bulkiness of the vindoline and the carbomethoxy substituent at C-18, there will be extreme severe steric crowdedness in the molecule if the piperidine moiety retains its boat conformation as found in (20). Hence, it is assumed that the piperidine constituent takes up a chair form in which C-1, C-7 and C-22 are substituted at C-2, N-6 and C-4 as equatorial groups. In this conformation, the carbomethoxy group at C-18 is oriented towards the saturated portion of cleavamine while the vindoline is pointed away. It has to be stressed that, besides the chair conformation of piperidine which has been confirmed by X-ray [82], this conformation (depicted in (39)) is a proposition built on a crude model. It is hoped that the observed chemical shift value will serve to verify this conformation or at least provide an alternative.

The unsaturated part of the dihydrocleavamine half of the dimer (39) is similar to that of 18β-carbomethoxydihydrocleavamine (20) and the carbon-13 chemical shifts may be assigned accordingly (Table 23). The carbon C-17 is shielded by 1.35 ppm as a consequence of the vindolinyl substitution on C-18 in the dimer. Multiplicities from sfor decoupling and typical chemical shifts identify the C-methyl carbon C-23, carbomethoxy methyl carbon

C-21, carbonyl carbon C-20 and the new quaternary carbon C-18 which is deshielded (α-effect of the vindolyl substituent) by 15.54 ppm when compared to that in (20).

The two methine resonances at 31.77 ppm and 28.65 ppm can be attributed to C-2 and C-4, respectively. C-4 is assigned because of the expected constancy of its chemical shifts in both dimers (39) and (40) while C-2 in these two molecules are expected to exhibit different chemical shift values due to the different substituents at C-18. The upfield shift of C-2 and C-4 may be due to the strain in the dimer especially in the piperidine ring which is held rigidly in the chair conformation.

The aminomethylene resonances at 54.11, 53.25 and 44.99 ppm are assigned to C-5, C-7 and C-19, respectively. A deshielding of 2.75 ppm observed at C-5 relative to that in 18β-carbomethoxydihydrocleavamine (20) is the net effect of the two opposing factors: (a) the strain of the piperidine ring in the dimer, and (b) the removal of the steric interaction between H-5 and H-1 which are present in the monomer (20). The small deshielding effect shown by C-7 can be explained by the elimination of the transannular repulsion at C-18 which formerly existed in (20). The steric interaction induced between C-19, C-8, C-20 and $C_{17} = C_9$ is expected to give rise to a shielding effect at C-19. Thus, it is the resonance at 44.99 ppm which is assigned to C-19 in (39) representing a shielding effect of 14.08 ppm compared to that in (20). Similarly, C-8 is shielded in (39) compared to (20) as a consequence of this steric interaction and therefore the methylene resonance at 22.28 ppm is assigned to this carbon. The three remaining methylene resonances at 36.52, 36.74 and 43.86 ppm must be attributed to C-1, C-3 and C-22. The carbon atom C-3 is expected to be deshielded relative to that in (20) as a result of the alkyl β-substituent effect. That is, the substituents at C-2 and C-4 are changed from axial and 'almost' axial, respectively, in (20) to equatorial in (39), thus yielding the larger β-substituent effect typically observed in the cyclohexanes.[42] Since the carbon resonance of C-3 occurred at 31.18 ppm in (20), it seems reasonable to assign the peak at 36 ppm to it in (39). The other peak in the same region may be assigned to C-22 which is in a relatively sterically free environment in the dimer (39). The remaining resonance (43.86 ppm) has to be due to C-1. This assignment implies a deshielding effect of 17.32 ppm at this site when compared to that in 18β-carbomethoxydihydrocleavamine (20). It is proper to point out that the large deshielding value arises not only from the vindolinyl substituent at C-18 in the dimer, but also from the change of conformation of the piperidine ring in these molecules. That is, the steric congestion between C-1 and C-5 found in (20) is eliminated in the dimer (39), and further deshielding effects may arise from the proximity of the oxygen atom in the methoxy group at C-16' of the vindolinyl portion. Obviously it is difficult to pinpoint the magnitude of the chemical shift value attributed by each effect, but it can be speculated that the magnitude of the β-effect of the vindolinyl substituent might be larger than other typical β-effect values (~9 ppm). A large β-effect (+12.30 ppm) was observed at C-1 in catharanthine (22) where the substituent is $\begin{matrix} N_6 \\ C_4 \end{matrix} > C5$ —— on ring closure. The complexity of the proton spectrum of the dimer precludes the use of proton selective decoupling experiments to confirm these assignments. Our analysis shows that the proposed molecular structure (depicted in (39) is the most stable conformer for the dimer.

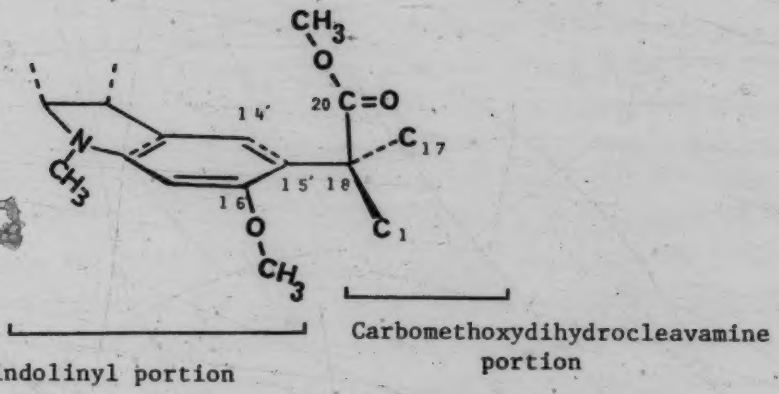
In the analysis of the carbon-13 data for the dimer (40), the vindolinyl and the indole ring portion of the dihydrocleavamine derivative are assigned by comparing with the chemical shift values obtained for vindoline (14) and dihydrocleavamine (18). These values are given in Table 23 and 26. Single frequency off-resonance decoupling and typical chemical shifts enable the distinction of the C-methyl carbon C-23, and the three methine carbons C-2, C-4 and C-18. The assignments of C-2 and C-18 are considered interchangeable. The small difference in chemical shift value in this case does not affect the analysis. C-18 exhibits a deshielding vindolinyl α-substituent effect of either 17.49 ppm or 14.79 ppm, depending on the assigned value. The size of this effect is comparable to that observed in dimer (39) (+15.54 ppm) suggesting the α-effect is mainly inductive in origin. The two remaining methines at 28.59 ppm and 36.09 (or 38.79) ppm are attributed to C-4 and C-2 respectively. It is apparent from a model that the vindolinyl substituent at C-18 does not impose any steric congestion in the dimer. It is possible that the cleavamine portion of the dimer retains the same conformation as that of dihydrocleavamine (18). That is, the piperidine ring is still in a boat form. It is evident from our analysis of the dimer (39) that it can serve as a means to verify this point. Comparison of the chemical shifts in dihydrocleavamine (18) and the dimer (40) shows C-4 in the dimer is shielded by 4.32 ppm. However, this carbon nucleus would not be expected to be affected sterically or inductively by the vindolinyl group unless a change in conformation occurred. Further the aminomethylene carbon C-5 is also deshielded by 2.37

ppm in the dimer (40) relative to that in (18). This change cannot be justified by the added substituent at C-18. A change in conformation in the piperidine ring of the cleavamine portion of the dimer must be invoked. This change would also explain the chemical shifts of the methylene resonances at 21.63, 35.77, 42.83 and 46.07 ppm which are attributed to C-1, C-3, C-8 and C-22. Since the chemical shift values exhibited by the dimer (40) are similar to those of the dimer (39), it seems highly possible that the dihydrocleavamine portion of both molecules have the same piperidine ring conformation.

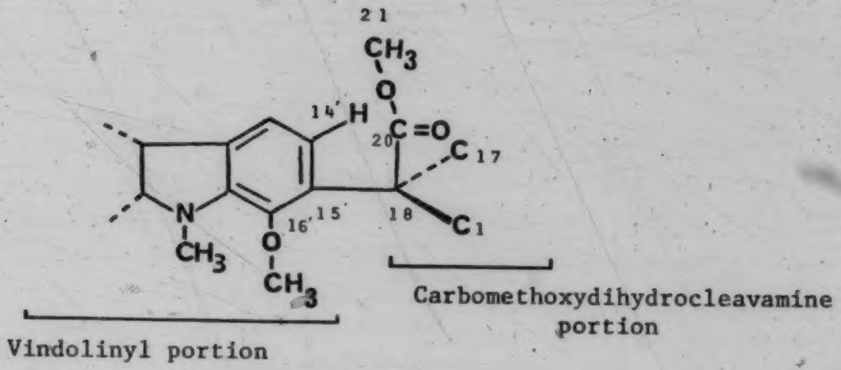
A few points of difference between the ^{13}C chemical shifts in the dimers (39) and (40) may be noted. The shielding of C-2 in the dimer (39) is reduced in (40) presumably as the result of removal of the carbomethoxy group at C-8 in (40) with consequent reduction of the steric congestion in the 9-membered ring. The carbon atom C-19 is deshielded by 8.24 ppm in (40), compared with (39), also the result of removal of the carbomethoxy substituent. The chemical shift at C-8 in (40) is less shielded (-12.19 ppm) than in (39) (-16.40 ppm) implying the reduced steric congestion in (40). The deshielding effect of 11.49 ppm at C-3 in (40) is large compared to that (+5.56 or +5.34 ppm) at the same position in the dimer (39). It is possible that the carbomethoxy group is oriented in such a way that the oxygen atom of the carbonyl carbon sterically hinders the position H-3 in (**39**). Moreover, we speculate that the plane of the indole portion of the vindolinyl substituent is perpendicular to the plane of the bond $C_{20} - C_{18} - C_{15'}$ in (**41**) since the chemical shifts of C-14' and C-16' of the vindolinyl part remain invariable in the two dimers. If the indole portion of the vindolinyl half and the bond $C_{20} - C_{18} - C_{15'}$ are on the same plane, either 14' or 16' in dimer (**39**) will be affected, depending on the orientation of the vindolinyl half, by the carbonyl carbon C-20 of the carbomethoxy group at C-18 in the dihydrocleavamine portion since steric crowding occurs between C-20 and either H-14' or the oxygen atom substituent at C-16' as shown in (**42**).

D. Conclusion

The complete analysis of the dimeric alkaloids described above is believed to be the first carried out. It is concluded that additivity parameters from suitably chosen model systems, modified in magnitude in order to compensate for the steric and strain requirement induced in the complex molecules, are valuable assets in the analysis of cmr spectra of alkaloids. It is suggested that these methods can be looked upon as guidelines for the cmr analysis of similar compounds. Our study also consolidates the accession of cmr spectroscopy as a tool


CH3
O
20
C=O
14'
N
CH3
C17
15'
18
16
O
CH3
C1
Carbomethoxydihydrocleavamine portion
Vindolinyl portion

41


21
CH3
O
14'
H
C=O
20
C17
N
16'
15'
18
C1
CH3
O
CH3
Carbomethoxydihydrocleavamine portion
Vindolinyl portion

42

in conformational studies of large molecules. This aspect is particularly significant for our dimeric species which are medicinally important and whose function seems dependent on the chair conformation of the piperidine in the dihydrocleavamine portion of the dimers.[82]

A few points can also be drawn from our present analysis: (a) the average carbomethoxy substituent α-effect is found to be +16.58 ppm in the cleavamines (19), (20) and (21), while the β-effects of the same substituent on the saturated carbon C-1 are found to be insignificant and deshielding (av. +0.31 ppm). The β-effects experienced by the indole quaternary carbon C-17 in these compounds are unexpectedly observed to be shielding (av. -2.86 ppm). (b) The vindolinyl substituent exerts a deshielding α-effect of 16.52 ppm (average of 17.49 and 15.54 ppm) at C-18 and an average deshielding β-effect of 1.73 ppm at the indole quaternary carbon C-17 in the dimers (39) and (40), but the β-effects of the same substituent observed at C-1 are more deshielding (+17.32 ppm in (39) and 19.86 ppm in (40)); the contributing factor in regard to the magnitude of these β-effects is mainly steric and inductive, and has already been discussed. (c) Large molecules, such as vindoline and dihydrocleavamines, can be used as model systems for the analysis of complex compounds. (d) Endocyclic homoallylic effects (av. -3.75 ppm) have been observed in the piperidine ring of (17) and (19). (e) In transformation from (19) to (22), the carbons (α and β) at and near the site of cyclization are generally deshielded, and (f) the inadequacy of employing N,N-dimethyltryptamine (33) as a model compound for the analysis of cleavamines has been revealed.

IV Carbon-13 NMR Analysis of Some Selected Strychnos Alkaloids

A. Introduction

The strychnos alkaloids, a group of dihydroindole alkaloids, have been subjected to the most intense chemical investigation in history since the discovery of the poison,strychnine, in 1819.[83] Their uses are limited to the induction of muscular relaxation and as a respiratory stimulant in modern medicine. A large time scale and numerous difficulties were encountered in the early strychnine chemistry when chemical degradations and synthetic studies were the chief sources of structural information.

The present cmr investigation of strychnine and its derivatives complements the other indole alkaloid study described in Chapter III and further demonstrates the value of the model compound studies (Chapter II) as aids in resolving complex structural assignments. The strychnos alkaloids were also chosen because of the challenge of their structural complexity, for example, strychnine, itself, contains 6 nuclear asymmetric centres and seven rings constituted from 24 skeletal atoms. The conformations of strychnine derivatives were investigated during the course of this study.

B. Experimental

Carbon-13 spectra were determined by the methods described in Chapter II. Pmr spectra were determined on a Varian Associates HA-100.

Strychnine and strychnine N-oxide were obtained from the Aldrich Chemical Company and were not further purified. Isostrychnine was prepared according to the method of Spiegel.[84] Dihydrostrychnine, dihydroisostrychnine, dihydrostrychnine methosulphate and strychnine methosulphate were synthesized by the procedure due to Robinson and co-workers.[85] Strychnic acid was obtained by the method proposed by Tafel.[86] Strychnine methiodide was made by direct combination of strychnine in chloroform and equal molar amounts of methyl iodide and was recrystallized from boiling water. Strychnine hydrochloride and dihydrostrychnine hydrochloride were prepared by allowing the bases to react with equal molar amounts of hydrochloric acid, the salts obtained were recrystallized twice from boiling water. The observed melting points of the above alkaloids along with their literature values are given in Table 27.

With the exception of strychnine methiodide, the common solvent employed for the carbon-13 nmr studies of these compounds was a mixture of deuteriochloroform and deuteriomethanol (2:1). 150 mg of compound in 1.8

TABLE 27

Melting Points of Selected Strychnos Alkaloids

Compounds	Values from this work	Lit. values
Strychnine	284-288°	284-286°[87]
Isostrychnine	213-216°	214-216°[85]
Strychnine hydrochloride	275-280°	-
Strychnic acid	179-182°	-
Strychnine N-oxide	200-202°	205-207°[88]
Strychnine methosulphate	284-288°	282°[85]
Strychnine methiodide	321-323°	320°[85]
Dihydrostrychnine	218-222°	220-222°[85]
Dihydroisostrychnine	247-251°	248-250°[85]
Dihydrostrychine hydrochloride	203-205°	-
Dihydrostrychnine methosulphate	315-320°	322°[85]

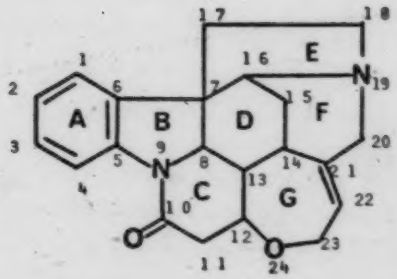
mls of solvent was used for each sample. Strychnine methiodide was run as a saturated solution in deuterio-dimethyl sulfoxide at 311°K. TMS was used as reference for all carbon-13 and pmr spectra.

C. Results and Discussion

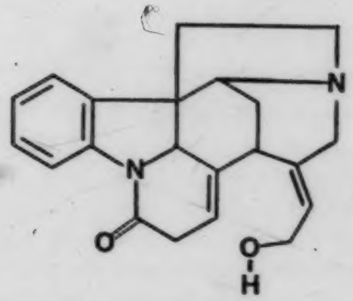
Names and structures of the strychnos alkaloids (43) to (53) are shown in Figure 15. The carbon-13 chemical shifts for these compounds are given in Table 28 and in correlation diagrams (Figure 16). The systematic numbering of carbon atoms in strychnine (43) was used throughout. Table 29 furnishes the proton chemical shift values used in the proton selective decoupling experiments. This analysis was carried out using the experimental methods described in Chapter II and similar assignment procedures and techniques employed in Chapter III.

The assignments of the carbon resonances in the parent molecule, strychnine (43), are chosen to illustrate the procedures and arguments leading to the unambiguous assignments of all the carbon resonances in this series.

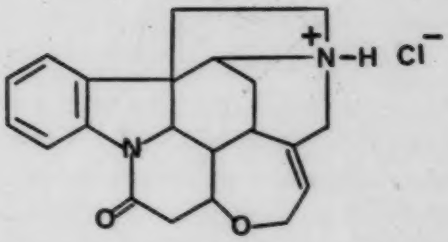
The decoupled spectrum of strychnine exhibits all 21 carbon resonances (Figure 17). The corresponding proton substitution pattern is revealed by sfor decoupled spectrum in the same diagram. There are nine resonances



Strychnine 43

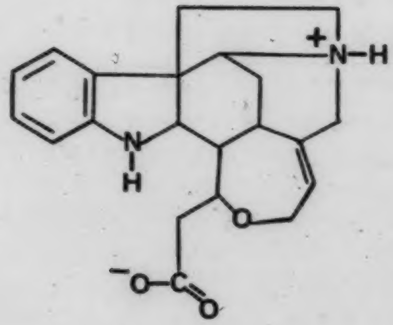


Isostrychnine 44

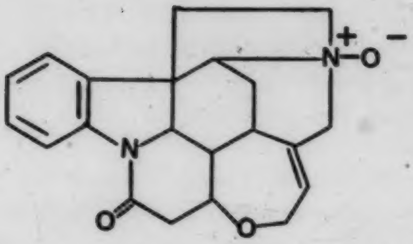


Strychnine hydrochloride 45

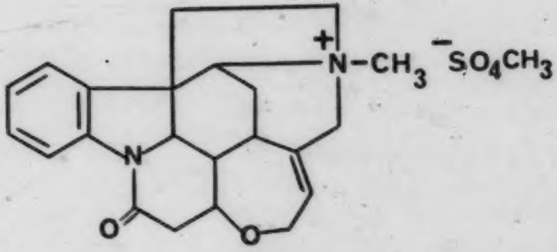
FIGURE 15 Names and Structures of the Strychnos Alkaloids Studied



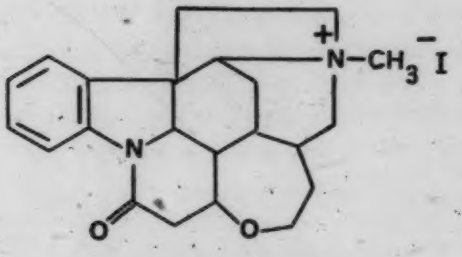
Strychnic acid 46



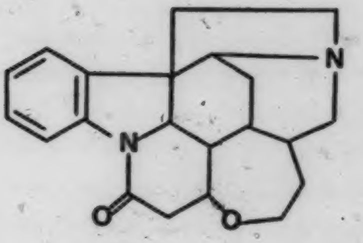
Strychnine N-oxide 47



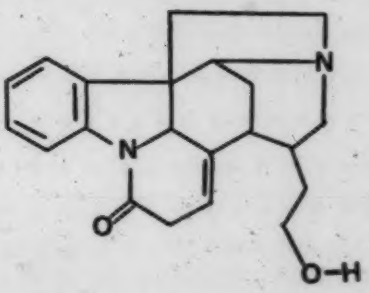
Strychnine methosulphate 48



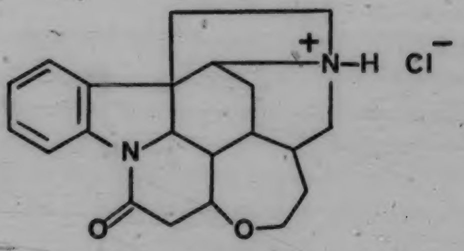
Strychnine methiodide 49



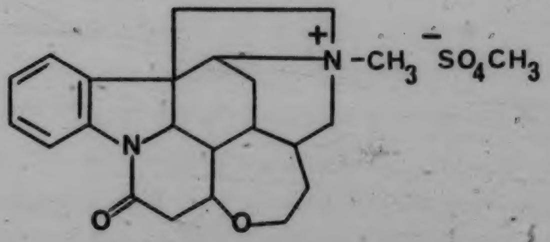
Dihydrostrychnine 50



Dihydroisostrychnine 51



Dihydrostrychnine hydrochloride **52**



Dihydrostrychnine methosulphate **53**

TABLE 28

Carbon-13 Chemical Shifts of Selected Strychnos Alkaloids[a]

Carbon Position	Compound										
	43	44	45	46	47	48	49	50	51	52	53
C-1	122.67	123.13	122.94	119.38	122.88	123.05	124.89	122.67	(122.64)	123.01	123.43
C-2	128.61	128.91	130.33	129.53	130.25	130.55	130.72	129.09	128.54	130.31	130.31
C-3	124.99	125.20	125.53	122.08	125.00	125.48	125.22	125.43	125.14	125.93	125.99
C-4	116.52	115.15	116.79	110.81	116.86	116.79	116.42	116.25	114.73	116.61	116.43
C-5	142.21	142.54	142.20	150.51	141.93	142.04	142.80	141.03	114.26	141.33	140.84
C-6	132.91	135.36	129.15	128.61	129.82	128.61	130.50	134.06	136.58	130.80	131.40
C-7	52.33	52.59	52.38	55.51	53.50	53.62	53.84	51.51	51.86	50.39	51.37
C-8	60.42	67.92†	62.31	61.07	58.79	59.07	59.40	67.43	70.78	65.85	65.92
C-10	170.31	169.93	170.04	178.02	170.96	169.99	170.21	170.63	169.87	170.60	170.42
C-11	42.46	37.01†	42.24	38.46	42.56	42.02	41.27	41.22	37.19	(40.90)	(40.29)
C-12	77.73	121.06†	77.31	86.85	77.36	77.19	76.72	76.66	(122.88)	76.51	75.65
C-13	48.44	136.94	47.42	46.46	47.84†	47.36†	47.42	53.30	142.26	52.34	52.53
C-14	31.83†	34.94	30.86	36.25	30.49	29.89	29.89	29.99	(36.15)*	29.03	28.91
C-15	26.92†	26.23	25.35	25.57	25.26	25.03	25.47	30.86	27.45	29.28	27.08
C-16	60.42	53.97	59.45	61.07	82.96	75.47	75.31	62.25	65.43	62.20	71.51
C-17	43.05†	46.50†	41.32	45.10	39.50	39.65	39.71	44.78	48.93	(41.14)	(40.96)
C-18	50.49	53.19	51.14	51.20	67.92	62.09	62.74	53.30	53.44	52.65	63.05
C-20	52.76†	54.29	52.54	52.92	70.36	64.47	64.58	56.86	54.72	55.26	65.25
C-21	140.04	141.51	132.65	135.19	135.24	132.87	133.85	34.85	(36.58)*	33.90	31.16
C-22	128.99†	127.45	136.54	134.65	135.00	137.24	136.70	32.48	35.30	31.34	31.16
C-23	64.84	57.88	64.41	68.03	64.25	64.47	64.90	68.62	59.65	68.34	67.44
C-19'						54.76	53.95				48.51
Other						54.76					54.85

a. In ppm downfield relative to TMS. † indicates assignment confirmed by proton selective decoupling. Parentheses and ( )* indicate the assignments are interchangeable within the molecule.

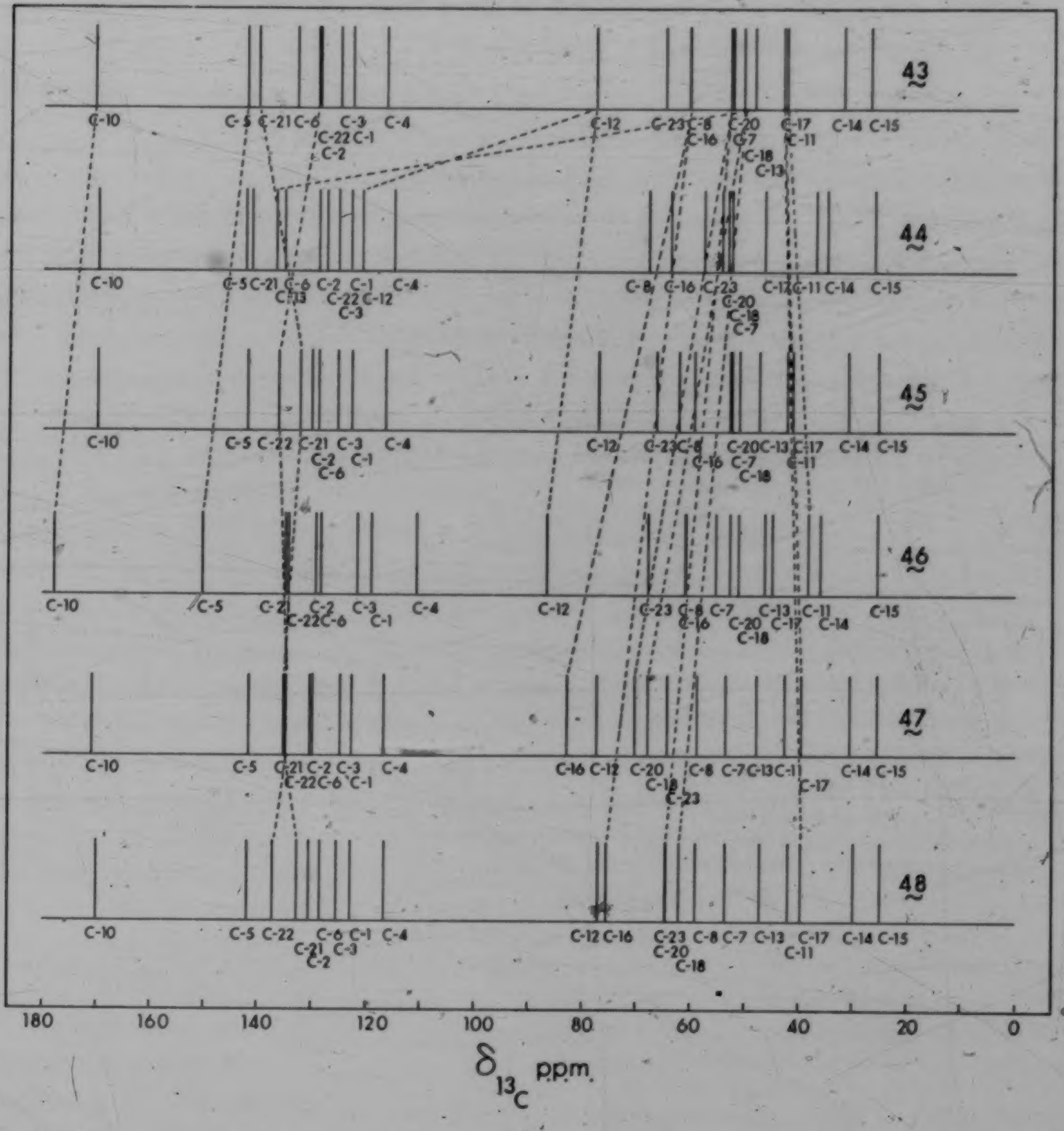


FIGURE 16. Carbon-13 Chemical Shift Correlations Showing Shifts and Assignments in the Strychnos Alkaloids Studied.

FIGURE 16 (continued)

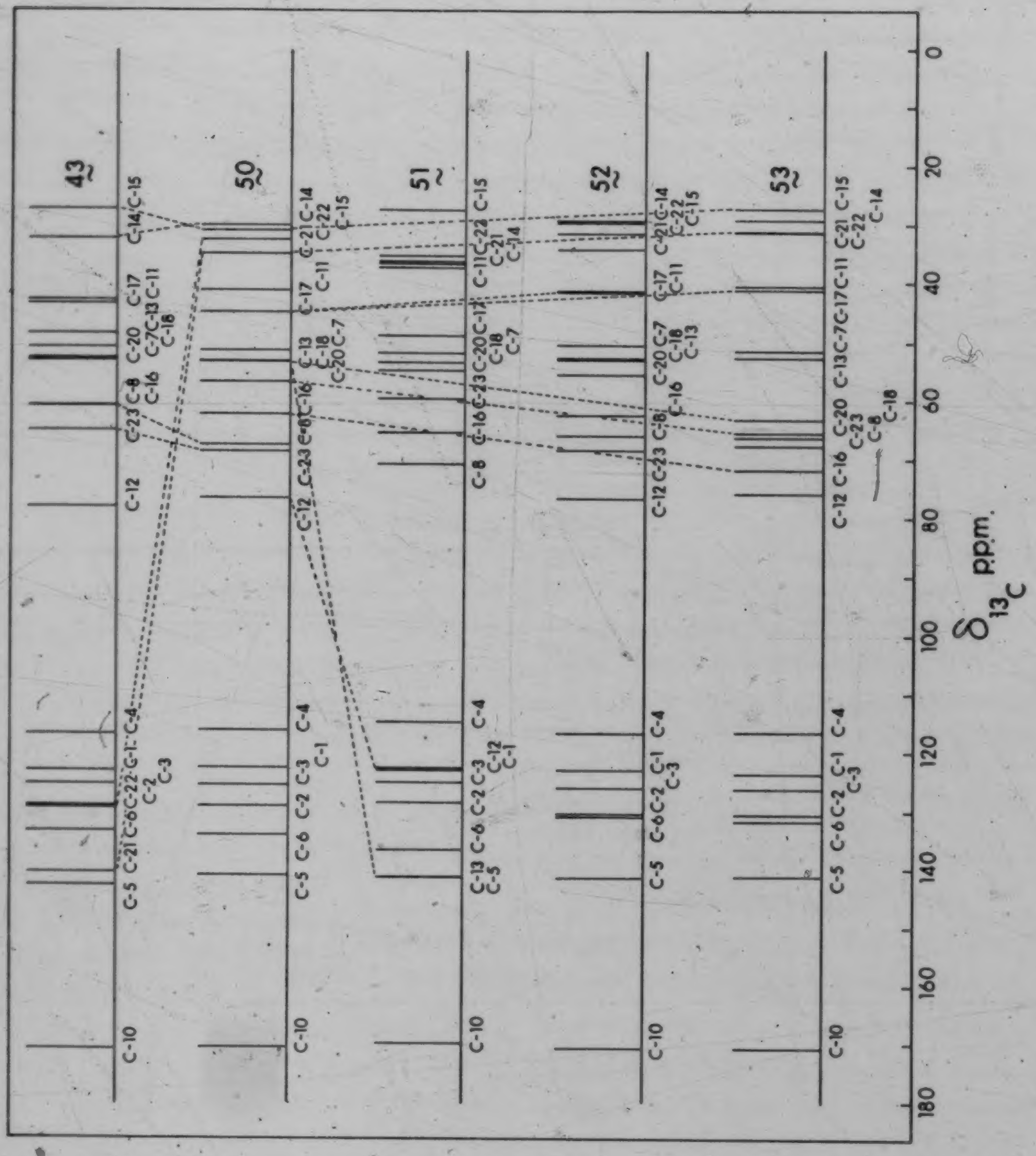


TABLE 29

PMR Chemical Shifts of the Protons Irradiated in Selective Decoupling Experiments of the Strychnos Alkaloid Studied[a]

Proton Position	Compound 43	44	47	48	50
H-8		4.2			
H-12		5.9			
H-13	1.3		1.4	1.4	1.5
H-15	2.4				
H-17	1.9	2.1			
H-18	3.1				
H-20	3.7				
H-22	6.9	5.6	6.4	6.6	
H-23		4.2			

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a. In ppm downfield from TMS.

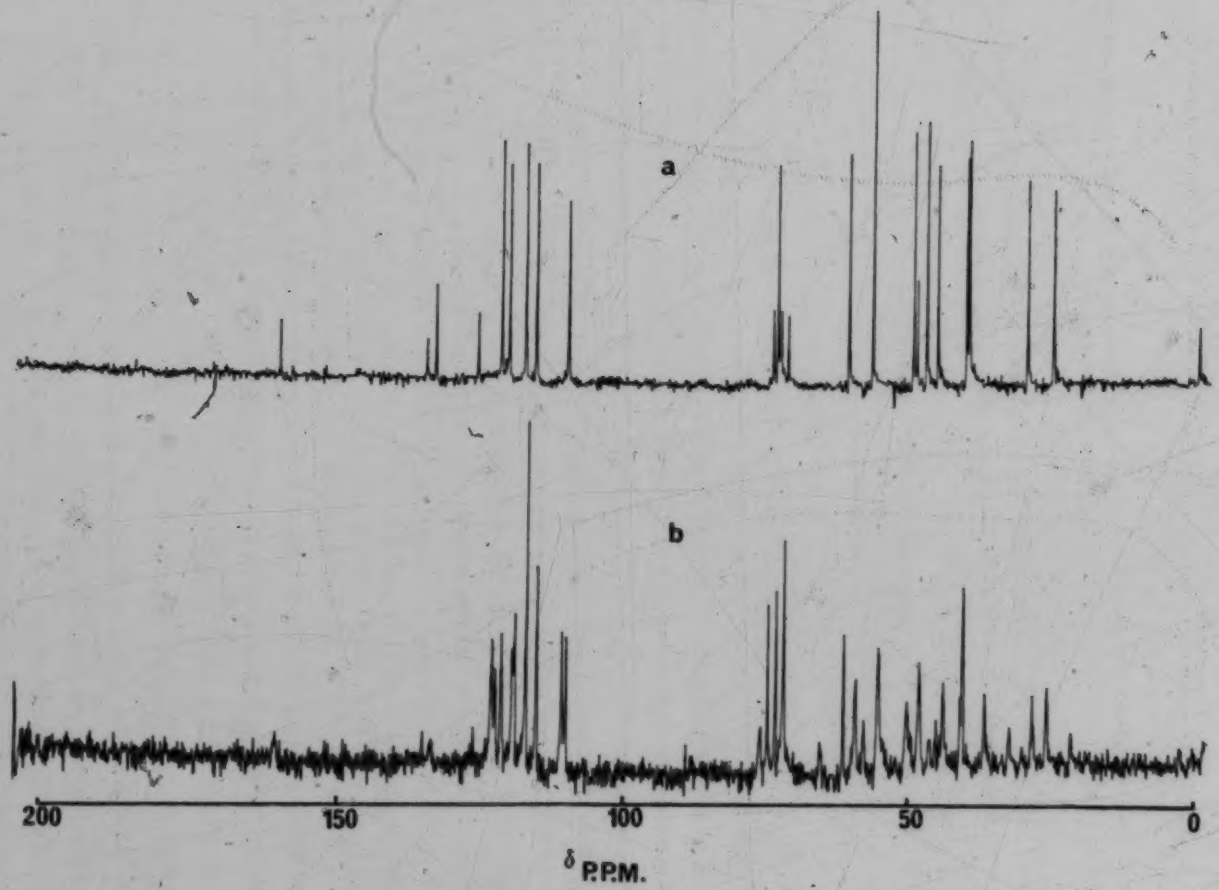
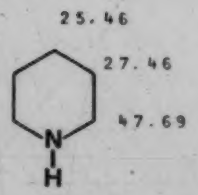


FIGURE 17. Carbon-13 NMR Spectrum of Strychnine (43) in Deuteriochloroform. (a) Noise Decoupled, and (b) Off-Resonance Decoupled.

corresponding to the unsaturated carbons at low field (110-170 ppm) and twelve due to saturated carbons at high field (20 - 80 ppm).

The following tentative assignments can be made on the basis of chemical shift theory and carbon type. Due to its characteristic shift, the most deshielded resonance is assigned immediately to the carbonyl carbon C-10. The unsaturated carbons in (43) may be assigned by analogy with the assignments made for indoles by Roberts[43] and our analysis of the cleavamines (Chapter III). The quaternary carbon C-5 is deshielded by ~10 ppm relative to the other indole quaternary carbon C-6 since the former is directly bonded to the electronegative N-9. The only quaternary signal in the high field region (52.33 ppm) of the spectrum may be attributed unambiguously to C-7. The most deshielded methine and methylene carbon atoms in this region are assigned to C-12 and C-23, respectively. These assignments are made since these carbons are directly bonded to the oxygen atom O-24. The greater electronegativity and hence deshielding effect of oxygen compared to nitrogen is shown by comparison of the α-carbon shifts in piperidine (54) and tetrahydropyran (55). The two aminomethine carbons C-8 and C-16 are assigned to the resonances at 60.42 ppm since they are adjacent to the electronegative and thus deshielding nitrogen atom. Similarly, the



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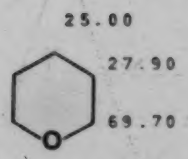

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resonances at 52.76 and 50.49 ppm can be assigned to the aminomethylene carbons C-20 and C-18, respectively. C-20 is assigned to the lower field resonance since the less rigidity (strain) of the 6-membered ring compared to the five favours this assignment. Furthermore, this carbon may be deshielded by the adjacent double bond $C_{21}=C_{22}$. The most shielded resonance at 26.92 ppm is assigned to C-15, one of the three remaining methylene carbons, because it is not adjacent to a carbonyl group as is C-11. Nor is it a neopentyl carbon centre as is C-17 which has already been found as the most deshielded carbon, except for the aminomethylene carbons, in the Aspidosperma alkaloid series.[78] Consequently, C-17 and C-11 are identified with the unassigned methylene carbon resonance at 43.05 and 42.46 ppm, respectively. The last two methine carbon resonances at 48.44 and 31.83 ppm have to be attributed to C-13 and C-14, respectively. The carbon atom C-13 is relatively more deshielded because it is β-substituted to N-19 and O-24.

In order to confirm the carbon-13 assignments in strychnine (43), a series of proton selective experiments were carried out. A 100 MHz pmr spectrum of strychnine and appropriate assignments are shown in Figure 18. These assignments were complemented considerably by the recently published and fully assigned 250 MHz spectrum of this compound.[89] The proton decoupling fequencies employed in the selective decoupling experiments are indicated by arrows. The results of these experiments prove conclusively that the C-13 chemical shift assignments in this parent molecule are unambiguous. The success of the analysis also emphasizes the chemical shift theory is adequate to correlate the chemical shift values of carbon nuclei even for a complex alkaloid.

Isostrychnine (44)

Introduction of a double bond at C_{12}-C_{13} position and ring opening of the 7-membered ring of strychnine (43) yields isostrychnine (44) which provides a different set of chemical shift values, particularly at the carbon nuclei which are directly affected by these structural changes. A new quaternary carbon (C-13) and methine carbon (C-12) resonances are expected to emerge in the low field region. The resonances at 136.94 and 121.06 ppm can readily be assigned to these carbons, respectively, and the assignment for C-12 has been confirmed by proton off-resonance and selective decoupling measurements. The remaining unsaturated carbon chemical shifts resemble closely those in strychnine (43). Carbon-13 nmr spectro-

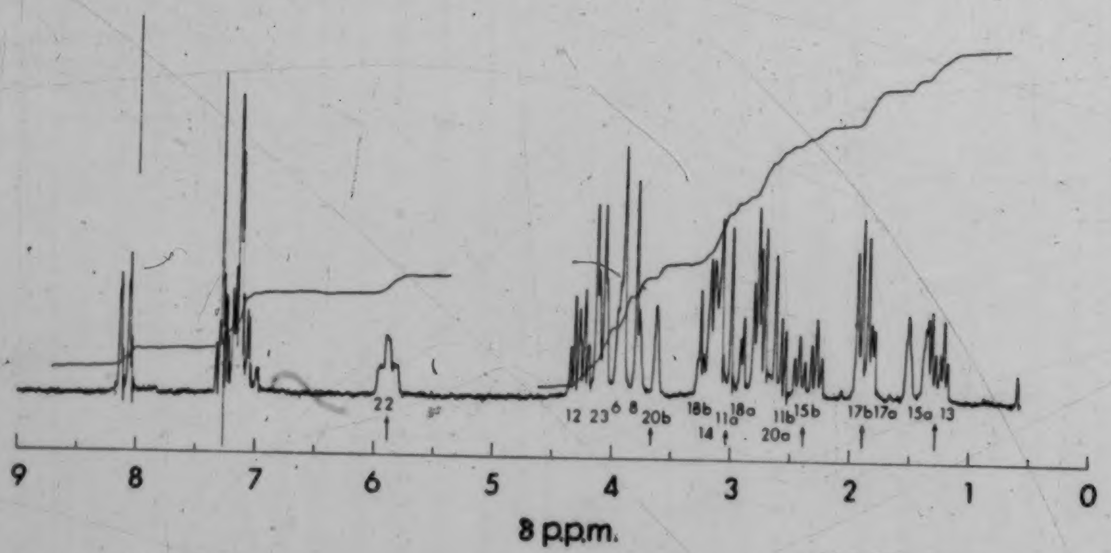
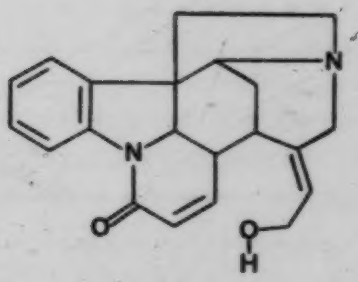


FIGURE 18. 100 MHz Proton NMR Spectrum of Strychine (43) in Deuterio-Chloroform.

scopy shows the presence of only one isomer of isostrychnine and proves that (44) is the correct configuration for the product obtained by the synthetic procedure employed. The presence of the other possible isomer (56), which would give two methine carbon signals due to C-11 and C-12 in the lower field region of the spectrum, is ruled out.



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Carbon-23 is shielded by 6.96 ppm on ring opening. The effect is apparantly due to the change of substituent from $-O_{24}-C_{12}$ (equivalent to methoxy) in strychnine (43) to hydroxyl in isostrychnine (44). This observation correlates with the fact that the methoxy group exerts a more deshielding α-effect than hydroxyl.[50] The methylene carbon C-11 is shielded by 5.45 ppm relative to that in strychnine (43) as a result of the removal of the substituent O-24 at C-12 and the α-effect of the double bond $C_{12} = C_{13}$, whereas the deshielding effect (+7.50 ppm) observed at C-8 can be correlated by the removal of the 1,3 syn-axial nonbonded interaction with O-24 which was previously present in (43), and the α-effect of $C_{12} = C_{13}$. The methine carbon C-14, which is also expected to be affected by these structural changes (from (43) to (44)), exhibits a downfield shift of 3.11 ppm in isostrychnine (44), compared to strychnine (43), mainly due to the incorporation of the double bond at $C_{12} - C_{13}$. Since the remaining unsaturated carbons resonate in similar regions as those in (43), it is reasonable to conclude that both alkaloids have similar conformation in the D,E and F rings. The downfield shifts at the sites C-16, C-17, C-18 and C-20 may be attributed to the small changes in conformation and strain between (43) and (44).

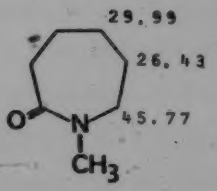
Strychnine Hydrochloride (45)

In contrast with the results observed for the protonation of monocyclic compounds in Chapter II (Table II), protonation has a smaller shielding β-effect in strychnine (43), the values obtained are -0.97 ppm, +0.65 ppm and -0.22 ppm at C-16, C-18 and C-20, respectively in strychnine hydrocloride (45). Applying the relationship between conformation and the γ protonation-effect found by Morishima [74] (described in Chapter II) to (45), one finds that only C-7 and C-17 give the expected shieldings (+0.06 ppm and -1.73 ppm, respectively) since the dihedral angle between the lone-pair of N-19 and $C_\beta - C_\gamma$ bond is ~120° in both cases in (43). The condition is similar to that in pyrrolidine hydrochloride which gives a γ-protonation-effect of -1.45 ppm (Table 9). The deshielding effect observed at C-7 may be correlated with the trend in which the protonation effect is more shielding at a secondary than at a quaternary carbon. The shielding observed at another γ-carbon C-15 cannot be rationalized by the path of protonation which, from models, is not perfectly 'folded". According to the dihedral angle (< 120° > 90°), the magnitude of the effect seems agreeable although the theoretical calculations [74] suggest a value greater than that observed at C-17 where the dihedral angle is 120°. The protonation effect (-7.04 ppm) exhibited by C-21 is large relative to that observed in piperidine hydrochloride (-4.91 ppm, Table 9) in spite of the conformational feature ('zigzag' path, and θ = 180°) being similar in both molecules. Our analysis indicates that C-22 in (45) is unexpectedly deshielded by 7.55 ppm, suggesting that the double bond $C_{21} = C_{22}$ is polarized by the protonated N-19 such that excessive charge density is located at C-21. From the pmr spectral data, it is believed that some electron density of H-22 is transmitted through the $C_{21}=C_{22}$ bond to C-21 as H-22 in (45) is relatively deshielded when compared with that in (43).

The resonance at 129.15 ppm is assigned to C-6 in strychnine hydrochloride (45) and this carbon is subsequently shielded by 3.77 ppm when compared with strychnine (43). The magnitude of this δ-effect enables the differentiation of C-6 and C-21 in (45) because C-6 in dihydrostrychnine hydrochloride (52) is also found to be shielded by 3.26 ppm on protonation. In addition, this carbon in other N-19 quaternized derivatives of strychnine also gives δ-effects of similar magnitude. These findings lead to the unambiguous assignment of C-6 in (45). The shielding δ-effects observed at C-6 and C-14 in (45) may be attributed to the intramolecular electric field effects[61] which are associated with the δ and ε protonation shieldings in monocycles described in Chapter II. The great protonation shift observed at C-6 may be correlated by the inductive polarization of π-electrons due to the protonated N-19 and, consequently, C-6 acquires more charge density on protonation. This speculation is also supported by the small downfield shifts of the remaining dihydroindole methine carbons.

Strychnic acid (46)

Carbon-13 chemical shift and infrared absorption data suggest that the Zwitterion (46) is the correct structure of strychnic acid obtained by the procedure employed. The strychnic acid Zwitterions is substantiated by the protonation at N-19 which is advocated by the observed chemical shifts of its vinyl quaternary carbon C-21 and methine carbon C-22. The former is shielded by 4.86 ppm while the latter is deshielded by 5.66 ppm relative to the corresponding carbons in strychnine (43). Similar observations were obtained in the assignments of these carbons in strychnine hydrochloride (45) and other N-19 quaternized derivatives of strychnine whose analyses will be discussed. The changes in chemical shifts (relative to those in strychnine (43)) observed in the dihydroindole portion are due to the change of substituents at N-9, that is, from $-N_9-\overset{O}{C}$ in (43) to -NH in (46). The calculated chemical shifts of (57) may be obtained from the shieldings of (58) and the methyl substituent parameters obtained for hexamethylenimine (Table 6). It is



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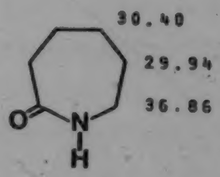

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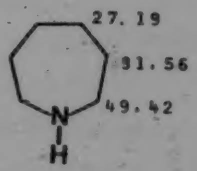

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apparent from the chemical shifts of C-2 and C-3 in (57) and (59) that the NH group has more deshielding β- and γ effects than $-N-\overset{O}{\overset{\|}{C}}$. Application of these findings to (46) suggests that C-5, C-8 and C-13 would be expected to be deshielded when compared to strychnine (43). Experimentally, C-5 and C-8 are deshielded by 8.20 and 0.65 ppm, respectively, and C-13 shielded by 1.98 ppm.

The carbonyl carbon C-10 is deshielded by 7.71 ppm when its substituent is changed from $-N\begin{smallmatrix} \diagup C_8 \\ \diagdown C_5 \end{smallmatrix}$ in strychnine (43) to OH in (46). This observation again confirms the fact that oxygen is more electronegative than nitrogen. If this difference of nitrogen and oxygen will influence the β-carbon, then C-11 is expected to be deshielded relative to (43). On the contrary a shielding effect of 4.00 ppm is observed at this carbon. This can be rationalized by the steric crowdedness between the protons of C-11 and N-9 in (46). This steric congestion did not exist in (43). C-12 which is two bonds remote from C-10 is not expected to be affected extensively by inductive polarization, but it is found to be deshielded by 9.12 ppm in the structural transformation from (43) to (46). Thus, it is speculated that this carbon may be deshielded by one of the oxygen atoms of the carboxylate anion which may be brought into close proximity with H-12.

N-protonation effects, in general, are less shielding in the Zwitterion (46) compared to those exhibited in strychnine hydrochloride (45). For example, the respective N-protonation shieldings for C-16, C-18, C-20, C-15 and C-17 in (46), along with those of (45) in parentheses are: +0.65 (-0.97), -0.71 (+0.65), +0.16 (-0.22) -1.35 (-1.57) and +2.05 (-1.73) ppm.

The deshielding effects shown by C-14 and C-23 may be interpreted by the reduced strain in the 7-membered ring in (46) relative to that in (43).

Strychnine N-oxide (47)

Oxidation at N-19 of strychnine (43) provides the N-oxide (47). In this compound C-21 is shielded by 4.87 ppm relative to the parent molecule (43). The γ-effect cannot be steric in origin and hence must be accounted for by the inductive effect of the quaternized nitrogen. The vinyl methine carbon C-22 shows a large deshielding effect (+6.01 ppm). Similar changes at these γ- and δ-carbons in both quaternizations (N-protonation and N-oxidation) indicate that the polarization of $C_{21} = C_{22}$ by the positively charged N-19 is reponsible for the observed chemical shifts of C-21 and C-22 in (45), (46) and (47). This phenomenon can be used to predict the chemical shift of C-22 in other quaternized N-19 derivatives of strychnine in this series. As in strychnine hydrochloride (46), C-6 is shielded by 3.10 ppm as a consequence of the oxygen substituent at N-19. Furthermore, the dihydroindole methines are slightly deshielded, suggesting the same inductive polarization of the π-electrons by the quaternized N-19 is operative in the molecule. The δ-carbons C-15 and C-17 are shielded by 1.66 ppm and 3.55 ppm, respectively, due to the substituent effects of oxygen at N-19. These values are less shielding than, but still comparable to those observed for simple rings in Chapter II (Table 15). The δ-carbon C-14 also exhibits the same trend as those in monocyclic compounds, while the β-carbons C-18 and C-20 are deshielded by 17.42 and 17.60 ppm, respectively. These values are large when compared with those of 1-methylpiperidine N-oxide (+10.37 ppm) in Chapter II. Since our present assignments for these two carbons in (47) are unambiguous, the results suggest that β N-oxidation effects are more deshielding in this molecule than in simple nitrogen monocycles. The methine resonance at 82.96 ppm is assigned to C-16 rather than to C-12 which is expected to remain unchanged in both strychnine (43) and its N-oxide derivative (47). Consequently, a deshielding β-effect of 22.54 ppm is suggested at C-16, paralleling the β-effect observed at C-18 and C-20. The remaining unsaturated carbons are assigned by correlation with the chemical shift values shown in strychnine (43). The invariability of these two sets of chemical shift values indicates that both (43) and (47) have the same conformation.

Strychnine Methosulphate (48)

The cmr spectrum of strychnine methosulphate (48) provides further analogies to the quaternization effects observed in (45) and (47), that is, C-21 is shielded (-7.18 ppm) and C-22 is significantly deshielded (+8.25 ppm). The quaternary carbon C-6 is also found to be shielded (-4.31 ppm) as in (45) and (47). Our analysis also shows pronounced β-effects due to the methyl substituent at N-19 in this system. Values of +15.05, +11.60 and +11.71 ppm are observed at C-16, C-18 and C-20, respectively. These values are large relative to those observed in the simple nitrogen heterocycles where a value of ~+9 ppm was more commonly observed. These experimental observations again indicate that caution must be employed in the use of substituent parameters derived from simple ring systems and applied to polycyclic complex molecules.

Carbons C-15 and C-17 show 'normal' shielding γ-effects (-1.89 and -3.40 ppm, respectively) due to the methyl substituent at N-19, but the other γ-carbon C-7 is deshielded by 1.29 ppm. Similar behaviour of C-7 is also observed in the hydrochloride (45) and N-oxide (47). This further indicates that, in spite of the different substituents at the quaternized nitrogen, the extent of polarization in the saturated portion of the alkaloid in inversely proportional to the degree of substitution of the carbon atoms, that is, the shieldings caused by quaternized nitrogen atom fall in the order of secondary > tertiary > quaternary. This may also explain the more deshielding substituent effect observed at the β-carbon C-16 (methine carbon) when compared to that observed at the other β-carbons C-18 and C-20 (methylene carbons) in (48) and (47). Finally, the consistent chemical shift values shown by the carbons of strychnine (43) and strychnine methosulphate (48) indicate that these molecules have the same conformation.

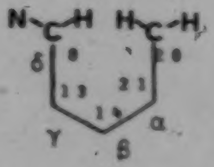
Strychnine Methiodide (49)

Methiodation at N-19 in strychnine (43) gives strychnine methiodide (49). Due to its low solubility in the solvent system employed in the study, deuteriodimethyl sulfoxide was used as solvent for this compound. Comparison of the observed chemical shifts in strychnine methiodide (49) with those in strychnine (43) and strychnine methosulphate (48) shows the same trend upon nitrogen quaternization. Carbons C-22, C-16, C-18 and C-20 are deshielded by 7.71, 14.89, 12.25 and 11.82 ppm, respectively, while C-21 is shielded by 6.20 ppm when compared with (43). On the basis of the observed chemical shifts, it is speculated that the structure and conformation of the cations of the methiodide (49) and methosulphate (48) are similar. The slight differences between the chemical shift values of (48) and (49) are attributed to solvent, concentration and temperature effects since the chemical shifts of the latter compound were determined as a saturated solution in deuteriodimethyl sulfoxide at 311°K while those of the former were obtained under the ambient experimental conditions.

Dihydrostrychnine (50)

Saturation of the olefinic double bond $C_{21} = C_{22}$ in strychnine (43) results in the loss of the quaternary carbon C-21 and methine carbon C-22 and provides the new methine (C-21) and methylene (C-22) carbons in dihydrostrychnine (50). The methylene carbon resonance at 32.48 ppm can be assigned confidently to C-22 in (50) whereas the assignment of C-21 is more difficult since there are three methine carbon resonance at 29.90, 34.85 and 53.30 ppm which may be attributed to C-13, C-14 and C-21. The effects of the double bond in the 7-membered oxygen heterocycles have not been investigated. However, we suggest that the effects are probably comparable to those observed in nitrogen heterocycles (see examples in Chapter III). Thus, C-14 is not expected to undergo any drastic shift because the effects of the double bond on allyl carbons in piperidines are only a few ppm as shown in Chapter III. Therefore it seems highly unlikely that C-14 would be deshielded by 13 ppm on saturation of the double bond $C_{21} = C_{22}$. Moreover, C-13 should be more deshielded than C-21 since the former carbon is β-substituted to both O-24 and N-9. Hence, the resonance at 53.30 ppm is tentatively assigned to C-13. The chemical shift data of dihydrostrychnine (50), to be discussed, suggest this assignment is correct. The proton spectrum of dihydrostrychnine (50) is more complex than that of strychnine (43). However, the multiplet at 1.5 ppm exhibits a splitting pattern and chemical shift similar to that due to H-13 in (43). Proton selective decoupling of this multiplet produced a sharp singlet at 53.30 ppm in the cmr spectrum of (50) confirming the assignment of C-13 in this compound. It is extremely difficult to differentiate the remaining methine carbons C-14 and C-21 as the effects of double bonds on allyl carbons are variable in nitrogen heterocycles (Chapter III). Unfortunately, additivity relationships cannot distinguish them because the calculations are complicated by various steric factors involved at these carbon sites. Nevertheless, the analysis of dihydrostrychnine methosulphate (53), to follow, suggests that the resonances at 29.99 ppm and 34.85 ppm should be assigned to C-14 and C-21, respectively.

The dihydroindole carbon chemical shifts in dihydrostrychnine (50) are similar to those of strychnine (43). This behaviour is expected since this portion of the molecule should remain relatively unperturbed. The analysis indicates that C-15, C-20, C-23, and to a lesser extent C-16, C-17 and C-18 are deshielded in (50) relative to the corresponding carbons in (43). The flexibility acquired by the saturated 7-membered and F rings may contribute to the observed effects, but the most significant deshielding effect (+7.01 ppm) exhibited by C-8 cannot be accounted for by the less strained condition in (50). Investigation of the causation of this large deshielding leads to the establishment of the conformation of this hydrogenated species. The basic approach to this problem is that a mole of hydrogen is added on the less sterically hindered side of the strychnine molecule such that the C_{20}-C_{21} bond is pushed upward providing a transannular repulsion between H-8 and H-20. The evidence for this proposed conformer is supplied by the large deshielding effect shown by C-8, which arises as a consequence of the removal of the 'almost' 1,3 syn-axial nonbonded interaction which was present between C-21 and C-8 in strychnine (43) and the acquisition of the deshielding δ-effect at C-8 due to C-20 (as depicted in (59)). Subsequently the downfield



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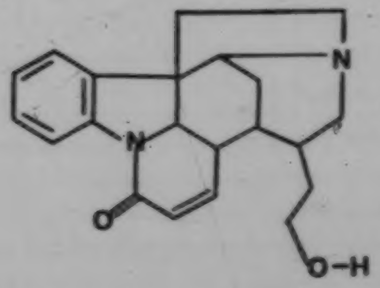
shift (4.10 ppm) observed at C-20 in (50), relative to (43), may be regarded as the net effect of the hydrogenation of the adjacent $C_{21} = C_{22}$ and the deshielding δ-effect due to C-8.

Dihydroisostrychnine (51)

In comparing the carbon-13 chemical shift data of dihydroisostrychnine (51) with that of dihydrostrychnine (50), it is easy to assign the quaternary carbon resonance at 141.26 ppm to C-13 and the methine carbon resonance at 122.88 ppm (or 122.64 ppm) to C-12. The presence of the quaternary and methine carbons confirm (51) as the correct structure for dihydroisostrychnine. The other possible isomer (60) is rejected on the basis of the carbon atom types demanded by this structure. It is apparent that the methine carbon resonance



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at 53.30 ppm assigned to C-13 in dihydrostrychnine (50) is shifted in the spectrum of (51), whereas the methine carbon assigned to C-21 is only deshielded by 1.73 ppm in (51). This observation further confirms the assignment of C-13 in (50).

The low field carbon shifts in the spectrum of dihydroisostrychnine (51), as expected, are similar to those in dihydrostrychnine (50). Carbon-23 in (51) is shielded by 8.97 ppm, compared to (50), as a consequence of ring opening. This effect was also observed between strychnine (43) and isostrychnine (44) and arises from the change of substituent from $-O_{24}-C_{12}$ to hydroxyl The methylene carbon C-11 in (5I) is shielded by 4.03 ppm, compared to (50) due to the α-effect of the double bond $C_{12} = C_{13}$ and the removal of O-24 at C-12. Again this effect is analogous to that found between (43) and (44). However, the magnitude of the deshielding effects observed at C-8 and C-14 in dihydroisostrychnine (51) is quite different from those observed in isostrychnine (44) when the two compounds are compared with their corresponding parent molecules. That is, C-8 in (51) is deshielded by 3.35 ppm in contrast to the 7.50 ppm exhibited by the same carbon in (44), while C-14 in (51) is deshielded by 6.16 ppm (or 6.59 ppm) as opposed to the 3.11 ppm shown by the same nucleus in (44). If similar structural and steric factors are involved in the transformations of (43) to (44) and (50) to (51), effects of similar magnitude are, thus logically, expected to be observed in both isostrychnine molecules. Since our assignments are regarded as unambiguous, the unexpected differences between the two sets of observed effects invoke reconsideration of the conformation of isostrychnine (44) proposed earlier. Apparently some conformational aspects of (44) are not clear without information on the analysis of the carbon-13 chemical shifts of dihydroisostrychnine (51). Because of the greater flexibility of F ring in (44) relative to (43), it is possible that the C_{20} - C_{21} bond in isostrychnine (44) is pushed upward such that there is transannular repulsion between H-8 and H-20. The structural arrangement of this part of the molecule is similar to that depicted in (59), the nonbonded interaction between the two syn-axial groups (C-8 and C-20) may be less than that observed in dihydrostrychine (50) as C-20 in (44) can move away from C-8. In this conformation, steric congestion is found between H-14 and the protons of C-23. The deshielding effect (+7.50 ppm) observed at C-8 can now be rationalized by the removal of the 1,3 syn-axial interaction between H-8 and O-24 which was present in strychnine (43), the α-effect of $C_{12} = C_{13}$ and the deshielding δ-effect at C-8 due to C-20 in isostrychnine (44). The less deshielding effect observed at C-8 in dihydroisostrychnine (51) may be attributed only to the removal of the similar 1,3 syn-axial nonbonded interaction between H-8 and O-24 which previously existed in dihydrostrychnine (50), and the α-effect of $C_{12} = C_{13}$. Hence the extra δ-effect that is experienced by C-8 in (44) is responsible for its more deshielding effect (+4.15 ppm) as compared to that observed in (51). The difference of 3 ppm between the effects observed at C-14 in the two isostrychnine molecules may be rationalized by the steric shielding induced between H-14 and the protons of C-23 in (44). This steric crowding is absent in (51) as the $C_{21} - C_{22}$ bond in (51) is free to rotate such that H-14 is free of any nonbonded interaction with C-23.

It is worthwhile to point out that the substitution pattern of the resonance at 53.44 ppm revealed by a standard sfor decoupled spectrum created some difficulties.

The off-resonance decoupled spectrum exhibits a doublet for this peak indicating the presence of a methine carbon, but chemical shift theory and the chemical shift values of the strychnines studied suggest that the resonance has to be due to one of the aminomethylene carbons, C-18 or C-20. A series of off-resonance decoupling experiments were subsequently carried out with different off-sets showing that the signal at 53.44 ppm is indeed due to a methylene carbon. It is apparent that complex spin splitting of the ABX system [78] involving the aminomethylene carbon gives rise to overlap in this region a standard off-resonance spectrum.

Dihydrostrychnine Hydrochloride (52)

The carbon-13 chemical shifts of dihydrostrychnine hydrochloride (52) show that dihydrostrychnine (50), in spite of its structural complexity, displays the protonation trend exhibited by the nitrogen monocycles (Chapter II). The β protonation-effects observed in (52) are comparable to those found for 5- and 6-membered heterocycles (Table 11). The values are -0.05, -0.65 and -1.60 ppm for C-16, C-18 and C-20, respectively. The tertiary carbon C-16, as expected, is less shielded than the other β-carbons C-18 and C-20 which are secondary carbons. Based on the model of (52), the path of protonation is 'folded' and the dihedral angle is 60° for both γ-carbons C-15 and

C-21. This situation is similar to that of 1-methylpiperidine hydrochloride. The protonation effect (-1.58 ppm) observed at C-15 in (**52**) resembles that obtained in 1-methylpiperidine hydrochloride (-1.70 ppm). The less shielding (-0.95 ppm) observed at C-21 in (**52**) can be rationalized by its higher degree of substitution. The γ-carbons C-7 and C-17 are shielded by 1.02 and 3.64 ppm, respectively. These values correlate with the dihedral angles of ~180°. The protonation shielding obtained at C-17 corresponds to that in piperidine hydrochloride in which the dihedral angle is also 180°. As expected,the quaternary carbon C-7 is less shielded than the secondary carbon C-17. The δ-carbons C-6, C-14 and C-22 are shielded by 3.26, 0.96 and 1.14 ppm, respectively. A similar protonation effect (-3.77) was observed at C-6 in strychnine hydrochloride (**45**). The shielding at C-6 in (**52**) denotes that the π-electrons in the dihydroindole portion may be polarized as in other N-19 quaternized strychnines. Similar to piperidine hydrochlorides, intramolecular electric field effects are speculated as the main contributor to the δ protonation-effects observed in (**52**). It has also been noted in the analyses of both hydrochlorides (**44**) and (**52**) that there is an alternating characteristic in their N-protonation effects which fall in the order of $\beta < \gamma$, $\gamma > \delta$. This feature appears to correspond with the theoretical prediction suggested by

Pople.[75] It is evident that the N-protonation shieldings found in (52) are highly conformationally dependent and sensitive to the degree of substitution of the carbon being effected. These findings further confirm the inductive polarization of the C-H bond to $\overset{\ominus}{C}-\overset{\oplus}{H}$ on protonation of the nitrogen atom as predicted by Pople [75] and Morishima.[74]

The remaining carbons in (52) are unaffected by the protonation at N-19 and are observed to resonate at similar regions to those in dihydrostrychnine (50). It is probable that (50) and (52) have the same conformation.

Dihydrostrychnine Methosulphate (53)

Dihydrostrychnine methosulphate (53) is expected to give similar methyl substituent-effects as those of strychnine methosulphate (48). The β-carbons C-16, C-18 and C-20, relative to the corresponding carbons in dihydrostrychnine, are deshielded by 9.26, 9.75 and 8.35 ppm, respectively. These values are attenuated, especially C-16, when compared with those observed in strychnine methosulphate (48), but resemble more closely those obtained in the monocycles described in Chapter II (Table 13). According to the crude model of (53), the methyl is expected to shield C-15 and C-21 as it imposes a slightly reduced 1,3 syn-axial steric interaction on these γ-carbons.

Experimentally, C-15 and C-21 are found to be shielded by 2.78 and 3.69 ppm, respectively. The carbon-13 chemical shift of the methyl group in (**53**) also indicates its sterically congested environment, since it is shielded by ~6 ppm compared to that in strychnine methosulphate (**48**).

The δ-carbons C-14 and C-22 give similar upfield shifts to those shown in 1,1-dimethylpiperidine (Table 13) and (**48**). Resembling other N-19 quaternized derivatives, C-6 displays a comparatively large shielding δ-effect (-2.66 ppm). Obviously, the positively charged N-19 effects this carbon site electronically in a consistent manner throughout the series of Strychnos alkaloids chosen. The analysis suggests that the methosulphate (**53**) and dihydrostrychnine (**50**) have the same conformation.

D. Conclusion

The preceeding section demonstrates that the cmr assignments of our selected Strychnons alkaloids can be sufficiently justified by chemical shift theory, additivity parameters, intercomparisons of chemical shift values of these structurally closely related molecules, and model compounds. This analysis also further accentuates the capacity of cmr spectroscopy as an analytical tool for structural and conformational investigation of highly complex alkaloids.

The prominent structural and conformational features of the strychnines studied revealed by their carbon-13 chemical shifts can be summarized as: (a) similar to 5- and 6-membered nitrogen monocycles, the N-protonation effects, in general, are found to be specific to the orientation of the electron lone pair of the nitrogen atom prior to protonation and the substitution pattern of the carbons. In addition, the N-protonation effects show alternating features corresponding to the alternation of the σ-inductive effects predicted by Pople[75]. (b) The large upfield shift of C-21 and downfield shift of C-22 observed in the N-19 quaternized strychnines may serve as a 'fingerprint' for similar types of strychnines. The observations suggest the inductive polarizations of $C_{21} = C_{22}$ and the $H_{22} - C_{22}$ bonds by the quaternized N-19. (c) Quaternization at N-19 shields the quaternary carbon C-6 and exerts a long-range polarization on the π-electrons of the dihydroindole moiety. (d) Relative to 5- and 6-membered nitrogen monocycles, the quaternizations due to N-methylation and N-oxidation have more deshielding effects in strychnine, that is, the β-effects are more deshielding, and the γ- and δ-effects are less shielding, but the same N-methylation in dihydrostrychnine gives substituent effects paralleling closely to those observed in monocycles. (e) The Zwitterion form was suggested for strychnic acid.

The success and ease in the course of assigning the chemical shift data to the proper carbon nuclei in these dihydroindole moieties spell out the fact that many difficulties encountered in the structural determinations in the early strychnine chemistry could be easily overcome if only cmr spectroscopy was available then.

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APPENDIX

4-t-Butylhexamethylenimine

A mixture of 81 cc of concentrated hydrochloric acid and 25 g (0.16 mole) of 4-t-butylcyclohexanone was stirred, cooled in an ice-bath and 16.2 g (0.25 mole) of sodium azide was added as rapidly as the evolution of nitrogen would permit. The mixture was stirred for 12 hours, sodium carbonate was added until the mixture was slightly alkaline and turned pink. Water was added to dissolve the inorganic salts, and the yellowish oil which had separated was extracted with chloroform. The extract was washed twice with 25 cc of distilled water and was dried over anhydrous sodium sulfate, the solvent was removed and the yellowish residue was purified by sublimation to give 4-t-butyl-7-ketohexamethylenimine which is a white solid; m.pt. 149-150°, yield 13.3 g (49%). 10 g of the lactum (0.06 mole), dissolved in 200 cc of tetrahydrofuran, was reduced with 3.8 g (0.1 mole) of lithium aluminum hydride. The mixture was refluxed for 35 hours. Water (15 cc) was added cautionsly from a dropping funnel to the stirred mixture which was maintained at 0°. After filtration, the filter cake was washed with chloroform. From the dried reaction solution 6.3 g (67%) of the imine was obtained; b.pt. 95-98° (10 mm). The pmr spectrum of the imine δ TMS ($CDCl_3$) 3.00 - 2.65 (broad, m, 4H) 2-1 (broad m, 7H) and 0.86 (s, 9H).

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.64; N, 9.02.

Found: C, 76.87; H, 13.98; N, 9.73.

1-Methyl-4-t-butylhexamethylenimine

13 g (0.08 mole) of 4-t-butylhexamethylenimine was added to 9.2 g (0.2 mole) of formic acid which was cooled by an ice-bath. 6.8 g (0.09 mole of formaldehyde) of 40% formaldehyde solution was added dropwise to the stirred mixture. The ice-bath was removed after the addition was completed. The mixture was allowed to warm up to room temperature and CO_2 began to evolve. After the evolution of CO_2 had ceased, the mixture was gently refluxed for 12 hours. To the cooled mixture was added 10 ml of 30% hydrochloric acid. Formic acid and excess formaldehyde were evaporated off. Saturated aqueous NaOH solution was added to the residue until the pH was approximately 9 and the imine separated as yellowish oily layer on the top. The product was extracted with chloroform (3 x 30 ml). The chloroform solution was washed twice with 20 ml of distilled water and dried over anhydrous $MgSO_4$, filtered, and the solvent was removed. The yellowish residue was distilled, b.pt. 76.5 - 77.0° (3 mm). 4.1 g (30%) of imine was obtained. The pmr spectrum of the imine δ TMS ($CDCl_3$) 2.70-2.38 (m, 4H) 2.30 (s, 3H), 2.00-1.15 (broad m, 7H) and 0.85 (s, 9H).

Anal. Calcd. for $C_{11}H_{23}N$: C, 78.02; H, 13.70; N, 8.28. Found: C, 77.87; H, 13.51; N, 8.03.

1-Methyloctamethylenimine

6 g (0.05 mole) of octamethylenimine was methylated with formic acid and formaldehyde in the manner described above for the preparation of 1-methyl-4-t-butylhexamethylenimine; b.pt. 77-78° (20 mm). The pmr spectrum of 1-methyloctamethylenimine δ TMS ($CDCl_3$) 2.65 - 2.25 (m, 7H) 1.55 (broad s, 12H).

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.03; H, 13.05; N, 9.87.

3-Methyl-3-azabicyclo[3.2.2]nonane

3-Azabicyclo[3.2.2]nonane was methylated by formic acid and formaldehyde by the same procedure for the preparation of 1-methyl-4-t-butylhexamethylenimine; b.pt. 57-58° (2 mm). The pmr spectrum of the imine δ TMS ($CDCl_3$) 2.56 (d, 4H) 2.3 (s, 3H) 2-1.35 (m, 10H).

Anal. Calcd. for $C_9H_{17}N$: C, 77.70; H, 12.23: N, 10.07. Found: C, 77.83: H, 12.39; N, 10.31.

1-Methyloctamethylenimine N-oxide

A solution of 4.31 g (0.025 mole) of m-chloroperbenzoic acid in chloroform was added gradually at 0-5° to an ice-cooled, stirred solution of 3.18 g (0.025 mole) of 1-methyloctamethylenimine in chloroform. Stirring was continued for 8 hours at 0-5°. The mixture was allowed to come to room temperature and passed through a column of alkaline alumina which weighed 150 g. The traces of unreacted amine were removed by washing with chloroform. Elution with methanol-chloroform (1:3) then gave 2.80 g (80%) amine N-oxide. A small portion of the N-oxide was allowed to react with 50% ethanolic solution of picric acid to give amine oxide picrate which was recrystallized from 95% ethanol; m.pt. 178-181°. The pmr spectrum of 1-methyloctamethylenimine N-oxide δ TMS ($CDCl_3$) 3.95 - 3.65 (m, 4H) 3.5 (s, 3H) 2.45 - 1.75 (broad m, 12H).

Anal. Calcd. for $C_{15}H_{22}N_4O_8$: C, 46.63; H, 5.70: N, 14.51; O, 33.16.

Found: C, 47.01; H, 5.98; N, 14.16; O, 33.54.

3-Methyl-3-azabicyclo[3.2.2]nonane N-oxide

3-Methyl-3-azabicyclo[3.2.2]nonane was oxidized with m-chloroperbenzoic acid in the manner described above for the preparation of 1-methyloctamethylenimine N-oxide. A small sample of the amine oxide was converted to picrate which was recrystallized from 95% ethanol m.pt. 236-240°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.21; N, 14.58; O, 33.33.

Found: C, 46.14; H, 4.95; N, 14.79; O, 36.28.

The melting points of the amine N-oxide picrates prepared for characterizations are summarized, along with their corresponding literature values (if available), in Table 30.

1,4-Dimethylhexamethylenimine

The compound had been synthesized by Grob and coworkers [95], but no physical constants were recorded.

TABLE 30

Experimental Melting Points of Some Amine N-oxide Picrates

Compound	Melting Point
1-methylpyrrolidine N-oxide picrate	200-205° (lit., 201-204°[97])
1-methylpiperidine N-oxide picrate	178-182° (lit., 180-185°[98])
1-methylhexamethylenimine N-oxide picrate	187-201° (lit., 200-202°[98])
1-methylheptamethylenimine N-oxide picrate	193-196° (lit., 191-192°[98])
1-methyloctamethylenimine N-oxide picrate	178-181° decomp.
3-methyl-3-azabicyclo[3.2.2]nonane N-oxide picrate	236-240° decomp.